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ORIGINAL ARTICLE

CORTISOL LOWERING ACTION AND CARDIOVASCULAR STABILITY OF ETOMIDATE: A COMPARISON WITH PROPOFOL IN CONTROLLED HYPERTENSIVES

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ABSTRACT: BACKGROUND: Etomidate suppresses corticosteroid synthesis in the adrenal cortex by reversibly inhibiting the enzyme 11-beta-hydroxylase, leading to primary adrenal suppression. Continuous etomidate infusion for sedation of critically ill trauma patients in intensive care units has been associated with increased mortality due to adrenal suppression. Etomidate has a favorable haemodynamic profile and is the preferred drug in hypertensive patients but is often not used for the fear of adrenal suppression. Propofol is a widely used hypnotic agent used for induction of general anaesthesia. **AIM:** To study and compare the haemodynamic profile, the extent of adrenal suppression and the side effects of etomidate and propofol. **METHOD:** Sixty controlled hypertensives, undergoing laparoscopic major gynaecological surgery were randomly allocated in a double blind manner to receive as an inducing agent etomidate (0.3mg/kg) (group E) or propofol (2mg/kg) (group P). Anaesthesia was administered according to the standard institutional protocol and residual neuromuscular block was reversed. All patients were sent to post anaesthetic care unit. Systolic, diastolic , mean blood pressure and heart rates were recorded pre-induction, post induction and at 5 minutes thereafter until 30 minutes. Incidence of pain on injection was noted during induction and myoclonus was observed just after the induction. Incidence of PONV was noted in all cases. Serum cortisol levels were measured pre-operatively, after completion of operation and 24 hours post operatively. **RESULTS:** Mean blood pressure decreased in 60% patients in group P. 15% patients in this group suffered hypotension immediately after induction and needed bolus iv infusion and /or phenylephrine. No patient in group E needed phenylephrine. Patients receiving etomidate had a lower serum cortisol concentration immediately after the operation than those receiving propofol, but no differences between the groups were observed 24 hours postoperatively. Incidence of pain on injection, myoclonus and PONV were higher in group E but was not statistically significant. **CONCLUSION:** Induction with etomidate is a better than propofol in controlled hypertensives undergoing laparoscopic major gynaecological surgery with no serious deleterious effects due to decrease in cortisol levels.

KEYWORDS: Etomidate, Propofol, Controlled hypertensives, Laparoscopic major gynaecological surgery.

INTRODUCTION: Etomidate and propofol are rapidly acting hypnotic drugs without analgesic activity.[1] Propofol is widely used for induction of general anaesthesia. Etomidate has not been used widely for induction as it lowers serum cortisol levels.[2] Administration of etomidate produces minimal changes in haemodynamics,[3] whereas propofol induction decreases arterial blood pressure by several mechanisms.[4] The mechanisms for decrease in blood pressure compensates for blood

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pressure surge in post-intubation period and during pneumoperitoneum formation in laparoscopic surgery. Yagmurdur et al. studied biochemical effects of propofol and showed that it has got a distinct advantage over other induction agents. Propofol has got a preventive role as it scavenges reactive oxygen species and their metabolites in case of anticipated hypoperfusion-reperfusion phenomenon, which occurs in laparoscopic surgery.[5] Thus, propofol appears to be an ideal induction agent for laparoscopic surgeries in ASA I and II patients, but, this vasodilator and down regulation of baroreceptor effect of propofol is markedly pronounced in ASA III elderly, hypertensive patients as the baroreceptor reflex are set at higher level in hypertensives.[6] Fall of mean arterial pressure, if more than 30% may jeopardize coronary circulation.[7] Laporoscopy itself increases blood pressure and in hypertensive this causes a deleterious effect on the already compromised coronary circulation. Hence an ideal induction agent for hypertensive patients who are posted for laparoscopic surgery needs to be investigated.

METHODS: After institutional ethics committee approval and informed consent, 60 ASA II and III patients listed for laparoscopic major gynaecological surgery were selected in a randomized fashion. This study followed a prospective, randomized, double blind design. The patients were systematically allocated in order to ensure equal number of patients in each group. The 1st patient was randomly chosen and allocated to the1st group (group E) using computer generated random number table. The following patient was automatically allocated to the subsequent groups in a clockwise manner ie. Group P. The order was frequently reversed to avoid bias. Hypertensive patients between 40 to 60 years of age, a BMI between 18.5 and 24.9 kg/m^2 and blood pressure of less than 150 / 90mm of Hg pre –operatively, controlled with medications were included in this study. Patient refusal, patients suffering from asthma and diabetes mellitus, patients having anticipated difficult intubation, or those who had history of allergy to any of the study drugs were excluded from the study. Hypertensive patients were controlled either by amlodipine alone 5mg (7/60) or 10mg (17/60) or with amlodipine and telmesartan40 mg (36/60). Hypertensive patients who were controlled on beta blockers were also excluded from the study. The syringes containing the drugs were prepared by an independent anaesthesiologist (Not involved in the study) to ensure a proper blinding procedure. Syringes either contained Etomidate 2mg/ml or Propofol 10mg/ml. Middle triglyceride chain preparation was used for both the agents. The syringes were filled with normal saline up-to 20ml for blinding purpose. All the patients were given alprazolam 0.5mg and pantoprazole 40 mg orally on night before and at 2 hours before the surgery. Monitoring of pulse rate, SpO_2, continuous electrocardiogram, $EtCO_2$, non-invasive blood pressure and bi-spectral index was done. Clotted blood samples of all the patients were drawn pre-operatively for measuring serum cortisol level. Ondansetron 0.15mg/kg mg i.v, glycopyrrolate 0.2 mg i.v and fentanyl 2µg/kg i.v was given. After pre-oxygenation, patients were administered either propofol (2mg/kg) or etomidate (0.3mg/kg) according to their group. Patients of both the groups were asked for pain on injection as well as visually observed for any withdrawal due to pain. After infusion of the drug, occurrence of myoclonus, if any, was noted. Succinylcholine in a dose of 1.5mg/kg was given for intubation. Anaesthesia was maintained with nitrous oxide and oxygen in a ratio of 2: 1 and isoflurane in a dial concentration of 0.6% and vecuronium as muscle relaxant. Intravenous paracetamol infusion of 100 mg was given before creation of pneumoperitoneum. Pneumoperitoneum was created and intra-abdominal pressure was set at 12mm of Hg. Any hypertensive episode that occurred in intra-operative period was managed by nitroglycerine drip. Continuous $EtCO_2$ monitoring was done throughout the procedure.

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Intraoperative depth of anaesthesia was maintained by bispectral index between 40 to 60. Intra-operative mean arterial pressure (MAP) and heart rate was measured at every 5 minutes interval. Any hypotension was managed by intravenous fluid bolus and or 100 to 200µg iv phenylephrine each time till MAP reached within normal limits. Any episode of bradycardia was managed by iv atropine 600µg. After operation, residual neuromuscular block was reversed with neostigmine and glycopyrrolate. Incidence of post-operative nausea vomiting was noted in all the cases. All the patients were then sent to post anaesthetic care unit. Clotted blood samples of all the patients were sent at completion of operation and 24 hours after the induction.

STATISTICAL ANALYSIS: All the data were presented as mean ± standard deviation (SD). Categorical data were described as number of patients (n). Physical characteristics, heart rates and mean arterial pressures were analyzed using unpaired t-test. All categorical data including phenylephrine requirement, pain on injection, myoclonus and post-operative nausea vomiting were compared using Chi-square test. All differences were considered significant at $p < 0.05$. Statistical analysis was done using SPSS 13.0.

RESULTS: Demographic data was similar between the two groups. [Table 1] Etomidate showed haemodynamic stability during induction as well as post-intubation period. Tachycardia and hypotension were more marked after induction with propofol.

Incidence of bradycardia was more with propofol but was not statistically significant and was well within normal physiological limits.

Table 2 compares the effect on heart rate and mean arterial pressure between the two groups. Mean arterial pressure and heart rate returned to pre induction levels after 15 to 20 minutes of induction. 8 in 30 patients of propofol group required phenylephrine in a bolus dose of 100µg to manage hypotension. No case in etomidate group required pressor support after induction. [Table 3] Incidence of pain on injection, myoclonus and post-operative nausea and vomiting were comparable in both groups [Figure 1].

Serum cortisol levels were comparable at pre-induction levels in both the groups. At the end of operation, there was definite fall in serum cortisol levels in etomidate group and difference between two groups was significant. During this period of adrenocortical suppression, cortisol levels remained within physiological range, though towards lower side. Again after 24 hours of operation, cortisol levels returned to normal level in etomidate group. [Table 4]

DISCUSSION: Etomidate has been compared to other induction agents in various studies and has been known to preserve the haemodynamics whereas propofol does not.[8,9,10,11] Various mechanisms are proposed for these differences in haemodynamic response of these drugs. Propofol has been shown to decrease preload,[12] afterload,[13] and myocardial contractility.[14] Several investigations have attributed the arterial and venous dilating properties of propofol with direct effect on vascular smooth musculature.[15] Propofol has been shown to decrease the baroreceptor reflex relating to blood pressure in human beings.[16] In contrast, etomidate preserves baroreceptor reflex mechanism.[17] An induction dose of etomidate given to cardiac patients results in very stable haemodynamics with almost no change in heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, stroke volume, cardiac index, or pulmonary and systemic vascular resistance.[1] However Propofol remains the most commonly used agent in

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hypertensives inspite of the possibility of precipitous hypotension due to the fear of adrenal suppression caused by etomidate.

Hypertensive patients specially those who are controlled on more than two drugs are more prone to hypotension on induction because their baroreceptor slope are set at higher levels.[18] Today, more and more such patients are posted for laparoscopic gynaecological surgeries and choice of induction agent is of utmost importance in these patients in order to prevent damaging the already compromised coronary artery.. Our study has conclusively determined that etomidate surpasses propofol as induction agent in these patients too.

While etomidate is popular because of its minimal effect on haemodynamic state, concerns have been raised about possible adrenal suppression and subsequent adverse effects. Etomidate inhibits the conversion of cholesterol to cortisol by a reversible and concentration dependent blockade of 11-β hydroxylase and to a lesser extent 17-α hydroxylase.[19] This can be detrimental if used for continuous infusion as in ICU patients where sedation is infused for days to weeks. After a single bolus injection adrenal suppression starts after about 30 minutes and can last upto 24 hours.[20] Etomidate is particularly controversial in patients with known or suspected septic shock.[21,22] In sepsis, steroids play lifesaving role and can be dangerous if their levels are inhibited iatrogenically. In our patients, who were not an emergency cases and were not having any kind of adrenal suppression or crisis pre-operatively, after a single bolus dose, decrease in cortisol levels was transient, within physiological limits and was well tolerated by patients without any steroid pre-treatment or supplement. Our results were consistent with that of Schenarts and colleagues who showed that after a bolus dose of etomidate, cortisol levels are reduced than pre induction level, but it remains within the physiological range throughout the period of adrenocortical suppression. Moreover they also showed that etomidate was associated with reduced cosyntropin stimulation response test after 3 hours of induction but it was back to normal after 12 hours of induction.[23] Lacoumenta et al. stated that inhibition of steroidogenesis was not associated with a significant effect on blood glucose, blood lactate and plasma non esterified fatty acid values. Even heart rate and arterial pressures were comparable in both etomidate and propofol group in the post-operative period when the difference in the plasma concentration between the two groups were greatest.[24] Thus, this transient inhibition of steroids does not adversely affect the patient.

Pain on injection and myoclonus were major side effect noted with etomidate as well as propofol. It was observed that major cause of pain was propylene glycol which was used as a solvent with etomidate. This side effect has been eliminated while retaining the profile of action by dissolving etomidate in lipofundin (Medium chain triglycerides).[25] Etomidate dissolved in lipofundin has similar physiological osmolality and is devoid of pain upon injection, post-operative thrombophlebitis or haemolytic effects.[26,27] Similarly, propofol in the newer middle chain and lower chain triglyceride emulsion showed no significant pain on injection.[28]

The other disturbing side effect is myoclonus especially with etomidate. 50-80% of patients may develop myoclonic movements after etomidate administration.[29,30] Incidence of myoclonus has decreased in the newer middle chain triglyceride (MCT) preparation as compared to propylene glycol preparation. Pre-medication with benzodiazepenes and opioids has been shown to reduce myoclonus.[31,32] In our study all the patients were pre-medicated with opioid and MCT preparation was used for both the groups. This explains such low incidence of myoclonus.

Propofol has a documented anti-emetic effect. In sub-anaesthetic doses propofol has been used to treat nausea and vomiting in various settings. Surprisingly, various studies have shown

comparable incidence of post-operative nausea and vomiting with etomidate and propofol, without any significant difference.[1,33] In our study too we found results for nausea vomiting comparable.

CONCLUSION: Etomidate is a good induction agent for controlled hypertensives and the adrenal suppression caused by a single dose of etomidate is transient and has little bearing on non immunocompromised patient.

Limitation: Studies on uncontrolled hypertensives need to be carried out extensively to properly evaluate the usefullness of etomidate as ideal induction agent in hypertensives.

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Table 1: Comparison of Demographic, Anthropometric and Clinical Parameters in Group P (Propofol, n = 30) and E (Etomidate, n = 30)

Parameters	Group P (Mean±SD) (n=30)	Group E (Mean±SD) (n=30)
Age (yrs.)	47.24±4.762	49.56±7.226
BMI (kg/m$^{2)}$	23.472±1.545	22.713±1.709
ASA physical status (II : III)	10:20	11:19
Duration of surgery (minutes)	108.62±13.144	112.16±14.745

Table 1

BMI = Body Mass Index

Table 2: Comparison of Mean Arterial Pressure (MAP) and Heart Rate at specified times in Group P (Propofol, n = 30) and Group E (Etomidate, n = 30).

Time		MAP in mm Hg (Mean±SD)		Heart Rate in beats/min (Mean±SD)	
		Group P	Group E	Group P	Group E
Pre - induction		102.3±6.75	99.62±7.24	92.33±10.7	89.57±9.3
Post -induction	0 min	79.23±4.30*	96.58±7.57*	78.33±11.7*	92.58±10.1*
	5 min	109.27±12.6	111.85±12.75	88.7±12.52*	98.88±9.21*
	10 min	95.6±8.1*	101.42±9.27*	92.33±13.69*	93.15±9.41*
	15 min	93.6±8.48*	101.5±13.33*	101.67±13.97*	92.46±10.25*
	20 min	97.23±8.54	100.19±12.78	98.13±12.98	91.23±10.75
	25 min	98.9±9.66	102.54±11.41	96.47±11.71	89.31±10.59
	30 min	99.63±8.73	100.92±8.61	94.47±11.07	89.31±10.48

Table 2

*$p < 0.05$ (significant)

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Table 3: Requirement of phenylephrine in Group P and Group E.

	Group P	Group E
No. of patients requiring Phenylephrine	8/30*	0/30*
Table 3		

*p < 0.05 (significant)

Table 4: Comparison of serum cortisol levels in µg/dl.

Time	Group P Mean±S.D (n = 30)	Group E Mean±S.D (n = 30)
Pre-operative	15.1±1.55	15.5±2.1
At completion of surgery	14.4±1.6*	10.19±1.41*
24 hours after induction	14.66±1.54	14.44±1.65
Table 4		

*p < 0.05 (significant)

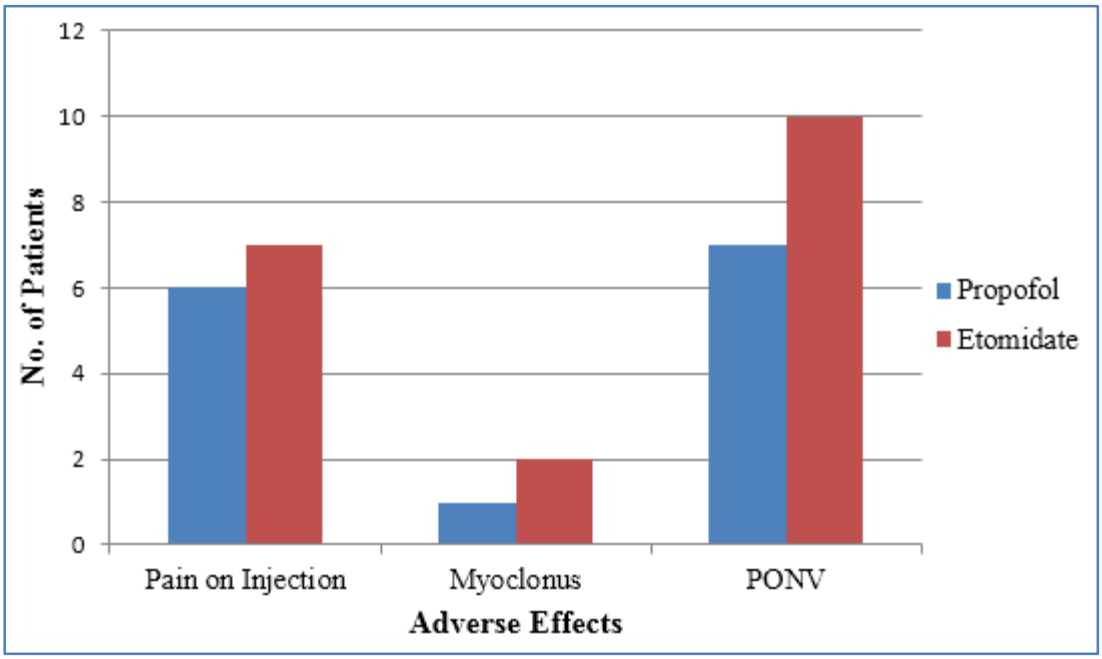

Fig. 1: Comparison of adverse effect profile

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