A Comparative Study of the Effect of Etomidate and Propofol Induction on Haemodynamic Response and Serum Cortisol Levels in Patients Undergoing Laparoscopic Cholecystectomy

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ABSTRACT

BACKGROUND

The choice of an anaesthetic agent for induction of anaesthesia is based mainly on its pharmacodynamic properties. We wanted to compare the effect of etomidate and propofol induction on haemodynamic response, serum cortisol level, and adverse effects in patients undergoing laparoscopic cholecystectomy.

METHOD

After approval from the institutional ethics committee, eighty-three American Society of Anaesthesiologist (ASA) grade I or II patients of 20-60 yrs. undergoing elective laparoscopic cholecystectomy were enrolled in the study. Patients were allocated randomly to receive either propofol or etomidate for induction of anaesthesia. Anaesthesia was maintained in both the groups with sevoflurane air and oxygen mixture, vecuronium bromide 0.08 mg/Kg for muscle relaxant.

RESULTS

The mean baseline haemodynamic parameters (SBP, DBP, MAP, HR) are comparable in both the groups. Post induction blood pressure was significantly lower in propofol group as compared to etomidate group. Immediately after intubation surge in blood pressure was more in etomidate group than propofol group. Also there was no difference in mean baseline serum cortisol levels in both the groups. But after induction, serum cortisol level was significantly decreased in etomidate group. However, after 24 hrs. of induction mean serum cortisol level in both the groups returns to baseline value.

CONCLUSIONS

Etomidate has more stable cardiovascular profile than propofol. It has the added advantage of minimizing induction hypotension which can cause coronary hypoperfusion, dysrhythmia and even cardiac arrest. Etomidate causes temporary reduction in serum cortisol level and this reduction in serum cortisol gets normalized 24 hrs. after induction.

KEYWORDS

Etomidate, Propofol, Serum Cortisol, Haemodynamic Parameters

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BACKGROUND

Induction of anaesthesia is a complex process, and is referred to the period of transition from an awake to an anaesthetized state.[1] Presently there are different types of induction agents available e.g. inhalational agent and intravenous agent. In modern day anaesthesia, intravenous agents are more commonly used to induce anaesthesia except in children where inhalational agent are preffered.[2,3] The choice of an anaesthetic agent for induction of anaesthesia is based mainly on its pharmacodynamic properties. Until now, cardiovascular effects were the main factor in this decision. However, other factors, such as the depth of anaesthesia and effects on cortisol synthesis, can modify this simplistic view. Since the introduction of general anaesthesia, no ideal inducing agent has yet been discovered in terms of providing stable haemodynamics during laryngoscopy and endotracheal intubation. Propofol, a short acting IV anaesthetic agent, is one of the most commonly used drugs for induction of general anaesthesia. Its recommended dose for induction is 1-2.5 mg/Kg and it produces unconsciousness within about 30 seconds.[4] Unwanted complication of propofol is haemodynamic instability and cardiovascular complication. It causes decrease in cardiac output and systemic vascular resistance due to inhibition of sympathetic vasoconstriction and impairment of baroreceptor reflex regulatory system. It also causes depression of myocardium and vasodilatation of cardiac vessels.[5-6] All this change can be detrimental to the elderly, hypovolaemic and patient with poor cardiac reserve. Etomidate is an ultra-short acting hypnotic agent which is cardiostable with no release of histamine. Unlike thiopental, propofol and midazolam, etomidate minimize induction hypotension, has minimal respiratory or cardiovascular effects and can be safely used in patients with hemodynamic instability or cardiac ischemia. It is cerebro protective with the ability to decrease intracranial pressure and maintain cerebral perfusion making it an ideal agent for patients with head injuries.[7-9] One of the rare but important side effect of etomidate is suppression of steroidogenesis by a reversible and concentration dependant block of 11-β-hydroxylase and 17-α-hydroxylase.[10-11] The resulting adrenal suppression reduces cortisol and aldosterone levels approximately 30 mins, after induction which may last upto 24 hrs. Adrenal suppression is a potential problem when etomidate is used as a continuous infusion agent for days or weeks in ICU settings but there are no reports of clinically significant cortisol suppression with single induction dose. Some studies have shown that the adrenal dysfunction is minimal with a single dose of 0.3 mg/Kg and resolves within 12 hours. Our study is conducted to allay the anxiety related to the use of etomidate as an inducing agent. In our study, the effect of single induction dose of etomidate is compared with that of propofol regarding the haemodynamic parameters and serum cortisol level. The incidence of adverse effects such as myoclonus, nausea, pain during injection and thrombophlebitis are also compared.

METHODS

This study was a prospective, randomized and double blinded design conducted in the Department of Anaesthesiology, JNIMS, Imphal, Manipur after approval from the institute's ethics committee. 83 patients aged between 20 to 60 yrs. of either sex and ASA status I & II scheduled for elective laparoscopic study were enrolled for the study. The patients were randomly divided into two groups of 43 each and randomization was done by computer generated random number tables.

After obtaining informed written consent, as part of the institute protocol, all patients were premedicated with ondansetron 0.15 mg/Kg and butorphanol 0.04 mg/Kg IV. Monitoring of NIBP, pulse rate, SpO_2, $EtCO_2$ and continuous ECG were done. Anaesthesia was induced with either propofol 2 mg/Kg or etomidate 0.3 mg/Kg according to their group. Patients were asked for pain on injection and were visually observed as well. Intubation was done with injection succinyl choline 1.5 mg/Kg, with appropriate size endotracheal tube after 3 min. of induction. Proper placement of endotracheal tube was confirmed by capnometry and bilateral auscultation of chest. Anaesthesia was maintained with air and oxygen mixture in a ratio of 4: 1, sevoflurane in a dial concentration of 0.8-2 along with intermittent bolus of vecuronium as required throughout the surgery. Intra-abdominal pressure was set at 12 mmHg after pneumoperitoneum. Intraoperative SBP, DBP, MAP and HR was measured before and after induction and thereafter at every 5 min interval starting from immediately after intubation up to 30 mints after intubation. After operation residual neuro muscular block was reversed with neostigmine 0.05 mg/Kg and glycopyrrolate 0.02 mg. Extubation was done after suction of oropharynx and adequate recovery. Serum cortisol estimation was done by collecting about 2 ml of clotted blood sample before induction of anaesthesia, after induction of anaesthesia (i.e. completion of surgery) and 24 hrs. after induction.

Statistical Analysis

The data collected was then analysed using statistical package for social science (SPPS Inc. Chicago 2, USA) window-based version 20. All the data was presented as mean ± standard deviation (SD), categorical data was described as number of patients (n). Physical characteristic such as HR, MAP, SBP, DBP were analysed using students t-test. All categorical data including mephentermine/ nitro-glycerine/ hydrocortisone/ glycopyrrolate requirement, pain on injection and post-operative nausea and vomiting were compared using chi–square test. All difference were considered significant at $p<0.05$.

RESULTS

The demographic characteristic namely, age, sex, weight and ASA status were similar in both the group.

	Etomidate (n=43)	Propofol (n=43)
Age (years)	40.05±11.58	40.77±12.57
Weight (kgs)	62.91±8.84	59.88±10.24
Sex (M/F)	9/34	9/34
ASA status I/II	31/12	35/8

Table 1. Demographic Profile

There was no difference in the mean baseline serum cortisol level in the two groups. There was significant reduction in serum cortisol, after induction in group E 6.66 ± 3.02 µgm/dl from baseline value as well as post induction value of group P (Table 2). But after 24 hrs. of induction the mean cortisol level in both the group (E = 8.32±3.24 and P = 9.25±3.32) return to baseline level and the difference between the two group is not significant (p>0.05) (Table 2).

	Group					
	Etomidate (n=43)		Propofol (n=43)			
	Mean	S.D.	Mean	S.D.	p	Significance
Baseline Serum Cortisol (in µgm/dl)	9.54	4.03	9.56	2.98	0.974	Not Significant
Post Induction Serum Cortisol (in µgM/dl)	6.66	3.02	8.62	3.49	0.007	Significant
Serum Cortisol After 24 Hrs (in µgm/dl)	8.32	3.24	9.25	3.32	0.194	Not Significant

Table 2. Mean Serum Cortisol Level in Both the Groups

The mean baseline SBP, DBP, MAP and HR in both the group was comparable. Significant decrease in mean SBP was seen in both the group just after induction and 5 mins. After intubation the fall in mean SBP was more in group P (post induction=106.35 ± 12.29 and 5 mins after intubation=117.93 ± 17.73 mmHg) as compared to group E and difference was statistically significant (p<0.05) .However, immediately after intubation mean SBP increases in the two group with a reading of 152.70±11.34 in group E and 146.30 ± 16.27 mmHg in group P. But after 10 mins of intubation mean systolic blood pressure was comparable in both the groups (Figure 1). The mean post induction DBP in group E was 80.95 ± 12.62 mmHg and in group P was 66.58 ± 10.80 mmHg. The decrease in mean DBP in propofol group is more as compared to etomidate group and is statistically significant (Figure 2). The mean MAP was 98.67±12.19 mmHg in etomidate group and 81.35±12.75 mmHg in propofol group just after induction. After 5 mins of intubation the MAP in group E was (98.14±11.81) and group P was (91.19±16.73) (Figure 3). But immediately after intubation (0 min), mean MAP increases with a value of 124.05 ± 14.51 mmHg and 113.14 ± 14.67 mmHg respectively for group E and group P. The increased in mean MAP was significant with p <0.002. However, after 10 mins of intubation the mean MAP of the two groups remains comparable (Figure 3).

Although not significant, mild increase in heart rate was seen in both the group after intubation from baseline. Thereafter, heart rate remains comparable in both the group and was slightly lower from the baseline value (Figure 4).

On comparing the adverse effect, it was found that myoclonus occur more frequently in etomidate group (7%) which is absent (0%) in propofol group**.** About 4.7% of patient in etomidate group complains of pain on injection while it is more in propofol group with a percentage of 18.6%. Nausea and vomiting were more prevalent in etomidate group (25.6%) as compared to propofol group which is 14% only (Table 3).

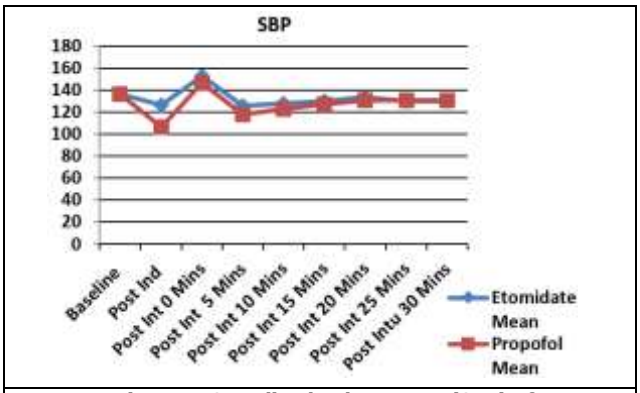

Figure 1. Systolic Blood Pressure (SBP) of Both Groups in mmHg

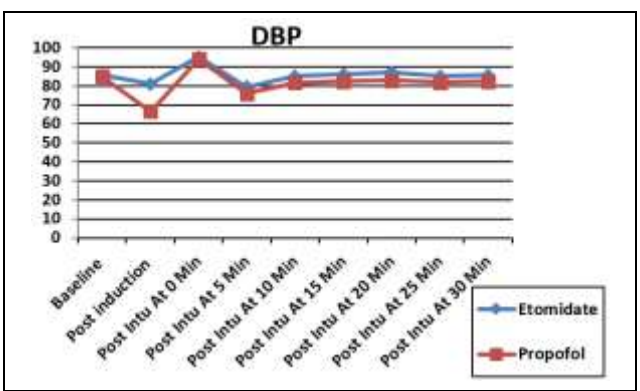

Figure 2. Diastolic Blood Pressure (DBP) of Both Groups in mmHg

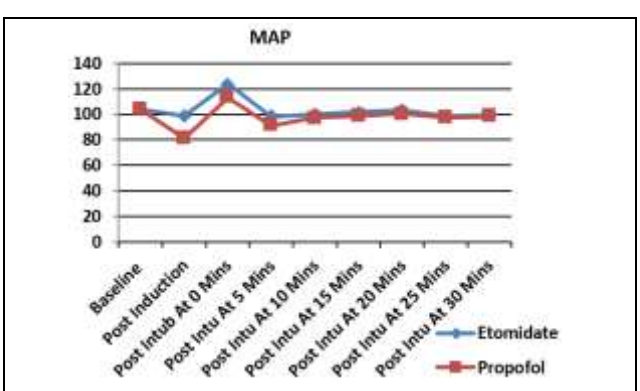

Figure 3. Mean arterial pressure (MAP) of Both Groups in mmHg

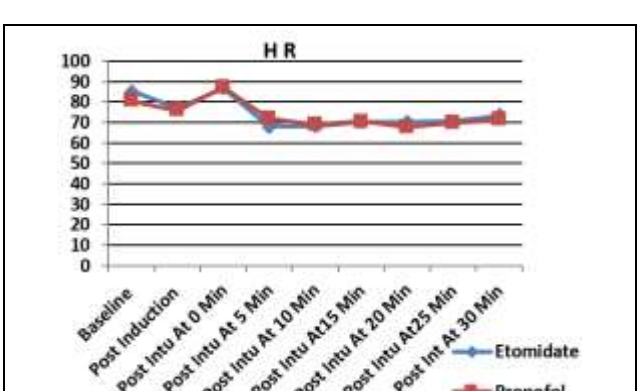

Figure 4. Heart Rate of Both Groups

Adverse Effect	Etomidate (N=43)		Propofol (N=43)	
	Yes	No	Yes	No
Myoclonus	7%	93%	0	100%
Pain on Injection	4.7%	95.3%	18.6%	81.3%
Nausea & Vomiting	25.6%	74.4%	14%	86.3%

Table 3. Adverse Effect Recorded in the Two Study Groups

DISCUSSION

In our study, the demographic data in both the groups were comparable. Also baseline haemodynamic parameters were also comparable in both the groups. But we observed a significant decrease in SBP, DBP and MAP after induction and 5 mins post intubation. This decrease was more in propofol than etomidate group and was statistically significant ($p<0.001$). This fall in blood pressure might be because propofol causes relaxation of vascular smooth muscle by inhibition of sympathetic vasoconstrictor nerve activity. In a study, Möller et al used propofol and etomidate in anaesthesia induction accompanied by BIS monitoring and found that propofol significantly reduced the MAP and delayed and inhibit the sympatho-excitation.[12] After intubation all the haemodynamic variables, SBP, DBP and MAP increases. The increase was significantly more in group E (152.7, 95.2 & 124 mmHg) as compared to group P (146.3, 93.8 & 113.4 mmHg). This might be because of the fact that etomidate does not inhibit sympathetic system. According to Ebert et al etomidate preserves both sympathetic outflow and autonomic reflexes.[13] This is in accordance with our findings of increased blood pressure following intubation in etomidate group. Singh R et al, observed that the etomidate was the least effective in minimizing stress response of intubation.[14]

Despite change in blood pressure, heart rate, in our study, was relatively comparable in both the group. This is in accordance with previous studies done by Baude C et al and Winn NN et al, which reported little or no change in HR with propofol or etomidate.[15-16] Regarding effect on steroidogenesis, it was observed that, serum cortisol level in etomidate group decrease significantly from baseline (9.54 to 6.66 mcg/dl). Also, the difference between the two group was significant ($p=0.007$). However, the decrease in serum cortisol was transient, within normal physiological limit and after 24 hrs of induction, serum cortisol gets normalized (8.32 mcg/dl). The decrease in level was well tolerated by the patient and the need of rescue regiment (i.e. inj. hydrocortisone), in any of the case was not required. This effect of etomidate is because of its ability to reversibly inhibit the enzyme 11β–hydroxylase in the pathway of steroidogenesis which is a rate limiting enzyme. Our study is in consistent with the findings of Pandey A. K. et al B who found that serum cortisol level on weaning the patient was significantly lower but still within normal level in the etomidate group (9.2 to 8.14 µgm/dl) as compared to propofol group (11.4 to 28.8 µgm/dl). The level of serum cortisol were returned to almost normal by 24 hrs.[17] CM Hohl et al, Sokolove P E et al, Hosten T et al etc also concluded the same result in their respective studies.[18,19,20] Side effect like pain was more common with group P (18.6%) as compared to group E (4.7%), and the difference was significant between the two groups. Our finding is in consistent with finding of Agarwal S et al, who did a comparative study between etomidate and propofol in 100 patient undergoing general anaesthesia.[21] Also study that favours our results are the study conducted by Jin wu et al, Ye L et al, Mayer et al. They all observed that incidence of pain was more with propofol group as compared to etomidate group.[22,23,24] The incidence of myoclonus was more in etomidate group (7%) and no myoclonus was detected in propofol group. Study done by James R minor for procedural sedation in emergency department found that myoclonus was noted in 20% of patient in group E and 1.8% only in group P.[25] In a study done by Alka Lunia et al in 100 adult patient undergoing general anaesthesia. They observed myoclonus to occur in 26% of patient in group E while no equivalent signs were noted in group P.[26] Doenicke AW, Roizen MF et al has reported incidence of myoclonus in 50 to 80 percent patients who did not receive any premedication with etomidate.[27] The incidence of myoclonus in our study was lower as compared to others studies. This can be due to use of butorphanol in the entire patient before induction. Slow administration of drug also explains the lower incidence.

In our study, incidence of nausea and vomiting and need of antiemetic administration was higher in group E (25.6%) than group P (14%), although the difference was not statistically significant. Our finding is also similar to the finding of Kumar A et al studies on propofol and etomidate as anaesthetic agent for elective non cardiac surgery where they found that there was no statistically significant difference in two group regarding nausea and vomiting.[28]

CONCLUSIONS

We conclude that etomidate provides more stable haemodynamic parameters (SBP, DBP and MAP) when used for induction of anaesthesia whereas propofol produced a significant fall in blood pressure after induction. This is because propofol causes vasodilation with larger reduction in arterial pressure, afterload and preload when compared to etomidate as an induction agent. Etomidate was less effective in minimizing stress response to intubation, with statistically significant increase in SBP, DBP and MAP from baseline ($p<0.05$). Although not significant, there was increase in heart rate also. This effect of etomidate is because of the fact that it does not inhibit sympathetic response to laryngoscopy and intubation.

Serum cortisol level in etomidate group decreases after induction significantly from base line ($p=0.007$). However decrease in serum cortisol was transient and within physiological limit without any adverse event. The level of serum cortisol gets normalized 24 hrs. after induction. Thus adrenal suppression effect of etomidate is temporary and reversible.

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