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Comparative effects of intravenous esmolol and lidocaine on bispectral index during propofol-fentanyl induction in patients scheduled for elective surgeries under general anaesthesia

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ABSTRACT

INTRODUCTION: Laryngoscopy and endotracheal intubation at induction of anaesthesia have been associated with awareness and haemodynamic fluctuations. Agents that can mitigate these effects should create better anaesthetic conditions. This study aimed to compare the effects of intravenous esmolol and lidocaine on the bispectral index (BIS) and haemodynamic responses during induction of general anaesthesia with propofol/fentanyl in adult patients scheduled for elective surgical procedures.

METHODS: This was a prospective randomized controlled study in ninety patients aged 18-65 years who were randomized into three groups to receive either IV esmolol 0.5 mg/kg, IV lidocaine 1.5 mg/kg or normal saline prior to induction of general anaesthesia.

RESULTS: The esmolol group had a significantly shorter induction time ($p<0.0001$) and a lower dose of propofol consumed ($p<0.0001$) than the lidocaine group. The mean pulse rate was significantly lower at the 1st min to 4th min post-intubation in esmolol and lidocaine groups compared to the control group (p values; 1 min= 0.005, 2 min= 0.008, 3 min= 0.023, 4 min= 0.018). There was a significant difference in the systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in the three groups at 2 min post-intubation.

CONCLUSION: Pre-induction intravenous esmolol 0.5 mg/kg was more effective than intravenous lidocaine 1.5 mg/kg in reducing the induction dose of propofol and the induction time. Esmolol also prevented increases in BIS better than lidocaine following endotracheal intubation but both agents were equally effective in attenuating the haemodynamic changes associated with laryngoscopy and endotracheal intubation

Keywords: Lidocaine, Esmolol, Propofol, Anaesthesia Induction, Bispectral index

INTRODUCTION

Achieving adequate depth of anaesthesia is an important goal during the conduct of general anaesthesia. When the depth of anaesthesia is inadequate, patients can become aware under anaesthesia and may have undesirable sympathetic stimulation leading to hemodynamic

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instability [1,2]. On the contrary, when anaesthetic depth is excessive, depression of the cardiovascular system may occur [2]. The incidence of awareness under anaesthesia has been estimated at 0.1-0.7% (1:142-1000), with approximately 4.6% occurring during the induction phase of general anaesthesia [3]. Other consequences of awareness during anaesthesia range from sleep disturbances to post-traumatic stress disorder (PTSD) in the postoperative period [3]. The Bi-spectral index (BIS) can measure the depth of anaesthesia, which reflects awareness when BIS is elevated and excessive depth of anaesthesia when it is reduced. Previous studies have demonstrated that the noxious stimulation of laryngoscopy and tracheal intubation was associated with increases in BIS, blood pressure, and heart rate [4,5]. Therefore, achieving acceptable BIS and haemodynamic stability during induction of anaesthesia is of utmost importance, especially in patients with higher risks of awareness, such as obstetric patients and patients with haemodynamic fluctuations, such as severe haemorrhage [6]. Hence, various ways of achieving adequate depth of anaesthesia at induction have been employed, including the use of adjuncts. Routray et al. [7] showed that esmolol, lidocaine, and fentanyl were equally effective in preventing haemodynamic fluctuations during laryngoscopy and intubation, whereas only esmolol and fentanyl prevented increases in BIS. Kim et al. [8] also did not show any evidence that lidocaine prevented BIS increases. Contrarily, Hans et al. [9] demonstrated a reduction of BIS following intravenous lidocaine.

Doses of esmolol at 0.5 mg/kg and lidocaine at 1.5 mg/kg have been shown to be free of major side effects [7]. Even at a dose between 1.5 mg/kg to 3 mg/kg, esmolol has been shown not to alter stroke volume or depress left ventricular function in patients with preserved cardiac function [10]. It has no or a very negligent effect on the alpha adrenoceptors; it does not affect peripheral resistance. An agent with both alpha and beta activity, such as labetalol, has been shown to have a more haemodynamic effect than a purely beta-blocker such as esmolol [11]. Lidocaine has been a popularly used agent for preventing pressor response during intubation; doses between 1.5-2.0 mg/kg have been studied for this purpose with no incidence of severe bradycardia or hypotension [7,12]. Routray et al. [7] and Jain et al. [12] used lidocaine 2 mg/kg, and no side effects were equally reported. However, a higher dose of intravenous lidocaine ≥4 mg/kg has been reported to be associated with most of the clinical side effects: tinnitus, circumoral numbness, dizziness, and hypotension [13].

This study compared the effects of esmolol at a dose of 0.5 mg/kg and lidocaine at 1.5 mg/kg on the BIS and the haemodynamic parameters (heart rate, systolic and diastolic blood pressure as well as mean arterial pressure) in adults that had elective surgical procedures with propofol/fentanyl induction.

METHODS

Study design: A prospective randomized, double-blind controlled study was then carried out on subjects with American Society of Anesthesiologists (ASA) physical status class I or II, aged between 18 and 65 years, who were scheduled for elective surgeries under general anaesthesia were recruited into the study.

Sampling technique: Patients were allotted into three groups E (Esmolol group), L (Lidocaine group) and C (Control group), using a simple random sampling technique (balloting). The randomization was done by a trained research assistant on the morning of surgery. Both the patient and the researcher were blinded to the group allocation. A total of ninety patients were recruited, 30 in each group.

Exclusion criteria are patient's refusal to participate in the study, obesity (body mass index > 30kg/m2), cardiovascular disease, pregnancy, patients with anticipated difficult airway, and patients with a history of allergy to propofol, esmolol, lidocaine or opioids.

Pre-operative assessment and preparation: A day before surgery, informed consent for the study was obtained from the patient by a trained research assistant (a registrar in anaesthesia), and a routine preoperative assessment was carried out.

In the theatre, pre-anaesthetic check was carried out, anaesthesia drugs were withdrawn and labeled, and baseline vital signs were taken (heart rate; systolic, diastolic, and mean arterial pressures; and peripheral oxygen saturation).

The study drugs (esmolol and lidocaine) were withdrawn according to patient's body weight into 10 ml syringes and diluted with sterile water to makeup 10 ml. The research assistant, after withdrawing the study drug, labeled the syringe

'study drug' and handed it over to the attending anaesthetist, who was equally blind as the researcher to the group allotted to the patient. The bi-spectral index sensor was attached to the patient's forehead, and the BIS value before induction was noted and recorded.

Induction of anaesthesia: Intravenous access was secured with an 18-gauge intravenous cannula, and 0.9% saline was commenced to run at 100ml per hour. After pre-oxygenation, the patients in group E (Esmolol group) received intravenous esmolol 0.5 mg/kg, and patients in group L (Lidocaine group) received intravenous lidocaine 1.5 mg/kg, while patients in group C (Control group) received 10 ml of normal saline intravenously (all solutions were administered over 2 minutes).

All patients were then given intravenous fentanyl 1 µg/kg for analgesia before intravenous propofol 1% was infused with a syringe pump at a rate of 300 ml/hour till a BIS value of 50 was achieved. The time to achieve this BIS value was measured with a stopwatch and recorded, as well as the dose of propofol.

Laryngoscopy and tracheal intubation were facilitated using intravenous suxamethonium chloride 1.5mg/kg, while the appropriate placement of the tracheal tube was confirmed by capnography and chest auscultation. Any patient who required more than one attempt at laryngoscopy and intubation was excluded from the study. Patients were thereafter maintained on isoflurane 1 vol% with 50% oxygen in air mixture, and muscle relaxation was achieved with 0.08mg/kg intravenous vecuronium.

The haemodynamic variables [pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)], SpO2, and BIS were recorded immediately before and after the study drugs were given, immediately after administration of IV fentanyl just prior to the commencement of propofol infusion. Thereafter, the haemodynamic variables (PR, SBP, DBP, MAP), SpO2, and BIS were recorded every minute during the propofol infusion until BIS of 50 was achieved. Post-intubation, the BIS values, PR, and SpO2 were recorded every minute, while the SBP, DBP, and MAP were measured at two-minute intervals for 10 minutes.

Side effects such as apnoea (cessation of breathing >10 seconds) prior to administration of suxamethonium, bradycardia (heart rate of <60 beats/min), and hypotension (SBP <90 mm Hg or a 35% decrease in MAP) were noted and managed appropriately. No surgical stimulation was allowed during the study period (induction to 10 min post-intubation). Thereafter, the patients' intraoperative and postoperative anaesthetic management was left at the discretion of the attending anaesthetist in line with departmental protocol.

Data analysis: Data were analyzed using the Statistical Package for Social Sciences SPSS software version 20 (SPSS Software IBM Corp., Armonk, NY, USA). Nominal data such as the presence or absence of hypotension, the use of ephedrine or atropine, and gender (male/female) were presented in frequencies and proportions and were compared using the Chi-square test. Continuous variables such as age, weight, SpO2, PR, MAP, dose of propofol, induction time, and BIS values were presented in means with standard deviations; associations in the three groups were compared using Analysis of Variance (ANOVA) test while association in between groups were determined by Bonferroni post hoc analysis. A p-value of <0.05 was considered statistically significant.

Ethical approval was obtained from the University of Ilorin Teaching Hospital Ethical Review Board.

RESULTS

A total of 90 patients (30 in each group) were recruited. All the patients who were randomized completed the study.

There was no significant difference in the demographic data and the ASA grading of the recruited patients, as shown in Table 1. The mean age was 43.10±13.83, 42.60±9.69, and 35.40±11.92 years in groups E, L, and C, respectively (p= 0.288). The gender and the ASA status were not significantly different across the three groups (p= 0.307 and 0.170, respectively).

The mean induction time to achieve BIS of 50 was 136.70±31.21, 159.60±8.58, and 184.20±23.16 s in the esmolol, lidocaine, and control groups, respectively. Intergroup analysis showed there was a significant difference only between the esmolol and control groups (p<0.0001)(Table 2).

The mean dose of propofol consumed to achieve the end-point for induction (BIS of 50) was 113.50±27.09 mg, 133.00±7.15 mg, and

Table 1: Comparison of patient's demographic data and ASA grading

Variable	Group E (n=30)	Group L (n=30)	Group C (n=30)	p value
Age (years)	43.10±13.83	42.60±9.69	35.40±11.92	0.288
Weight (kg)	63.10±6.17	68.10±5.15	62.40±5.56	0.065
Height (m)	1.66±0.76	1.68±0.06	1.64±0.06	0.449
Gender Ratio (M:F)	14:16	15:15	17:13	0.307*
ASA (I/II)	13:17	16:13	15:15	0.170*

*Mean ±SD (ANOVA). *Frequency and proportion (Chi-square). E- Esmolol, L- Lidocaine, C- Control, kg- kilogram, m- metre, M- male, F- female. ASA- American Society of Anaesthesiologists*

153.50±19.30 mg in groups E, L, and C, respectively (p-value< 0.0001; Table 2). Bonferroni post hoc analysis between groups only revealed a significant difference between groups E and C (p< 0.0001).

group L, 90.00±3.74 (p <0.0001) than groups E and C (Table 3). The BIS value was significantly lower in the lidocaine group in the first minute of propofol infusion than the control group (p= 0.045)

Table 2: Comparison of induction dose of propofol and induction time

Variables	Group E	Group L	Group C	p value E vs L vs C	E vs L	E vs C	L vs C
Dose of propofol consumed (mg)	113.50±27.09	133.00±7.15	153.50±19.30	**<0.0001***	0.105	**<0.0001***	0.082
Induction time (s)	136.70±31.21	159.60±8.58	184.20±23.16	**<0.0001***	0.103	**<0.0001***	0.072

Mean ±SD.: p value <0.05 (ANOVA, Bonferroni post hoc analysis). E- Esmolol, L- Lidocaine, C- Control. mg- milligrams, s- seconds*

There was no significant difference in the mean baseline BIS values in the three groups. The BIS values recorded at pre-induction (immediately after administration of drugs) were the lowest in

Following intubation, the BIS values were significantly lower from the first to tenth-minute post-intubation in group E compared to groups L and C (Table 3). A statistically significant difference

Table 3: Comparison of mean BIS values

BIS	Group E	Group L	Group C	p value E vs L vs C	E vs L	E vs C	L vs C
Pre intubation							
BIS Baseline	97.50±0.71	97.00±1.15	97.40±0.97	0.478	0.764	1.000	1.000
BIS after study drug	96.30±1.49	90.00±3.74	97.40±1.07	**<0.0001***	**<0.0001***	0.948	**<0.0001***
1st min propofol infusion	80.20±9.89	77.10±4.79	85.80±6.84	**0.045***	1.000	0.316	**0.044***
2nd min propofol infusion	66.20±11.59	64.70±4.64	66.40±6.96	0.882	1.000	1.000	1.000
Post intubation							
1 min	47.40±5.10	53.80±4.47	63.10±6.47	**<0.0001***	**0.040***	**<0.0001***	**0.013***
2 min	48.90±5.59	56.20±4.13	62.90±3.16	**<0.0001***	**0.003***	**<0.0001***	**0.020***
10 min	51.30±4.95	57.10±3.14	56.20±3.86	**0.003***	**0.010***	**0.007***	1.000

*Mean±S.D. *:p value <0.05 (ANOVA, Bonferroni post hoc analysis. E- Esmolol, L- Lidocaine, C- Control. BIS- Bispectral Index*

Table 4: Pre-intubation Pulse rate and Blood pressure

	Group E	Group L	Group C	p value E vs L vs C	E vs L	E vs C	L vs C
PULSE RATE							
Baseline	95.00±15.93	89.90±24.41	95.70±17.98	0.776	1.000	1.000	1.000
At BIS 50	79.70±11.91	87.80±19.78	97.30±16.69	0.074	0.842	0.072	0.623
SYSTOLIC BP							
Baseline	139.60±13.18	129.60±12.71	143.00±13.92	0.082	0.311	1.000	0.097
At BIS 50	115.50±13.99	116.20±11.75	121.20±10.72	0.532	1.000	0.920	1.000
DIASTOLIC BP							
Baseline	88.60±10.63	87.60±12.05	86.40±11.03	0.129	0.117	1.000	0.880
At BIS 50	70.50±11.94	68.10±8.51	73.80±4.64	0.165	1.000	0.850	0.510
MEAN ARTERIAL PRESSURE							
Baseline	104.20±11.24	100.70±10.54	105.60±10.58	0.248	0.178	1.000	0.061
At BIS 50	88.50±10.66	86.60±9.25	92.80±6.03	0.053	1.000	0.137	0.084

E- Esmolol, L- Lidocaine, C- Control. BIS- Bispectral index, BP- Blood pressure

between groups L and C was only seen in 1st to 3rd min post-intubation (p values; 0.013, 0.020, and <0.0001, respectively).

Changes in haemodynamic variables

The pulse rate recordings at each time point during the pre-intubation period showed no significant difference (Table 4). However, the first minute to fourth-minute post-intubation showed significant differences in mean pulse rate among the three groups, with group C having the highest values and group E the lowest (p values; 0.005, 0.008, 0.023, and 0.018, respectively (Table 5).

There was no significant difference in the systolic, diastolic, and mean arterial pressure before intubation. At two minutes post-intubation, group C had a statistically significant rise in systolic, diastolic, and mean arterial pressures (Table 5).

Table 5: Comparison of Post-intubation Pulse rate and Blood pressure

		Group E	Group L	Group C	p value E vs L vs C	E vs L	E vs C	L vs C
Pulse rate								
	2 min	93.50±16.02	96.40±19.22	118.60±10.71	**0.008***	1.000	**0.008***	**0.023***
	10 min	96.80±16.94	97.30±18.29	104.20±10.06	0.501	1.000	0.888	0.987
Systolic BP	2 min	129.30±10.56	128.30±11.29	152.60±11.49	**<0.0001***	1.000		**<0.001***
	10 min	112.20±11.48	104.40±14.03	121.00±13.86	0.240	0.428	0.441	1.000
Diastolic BP	2 min	80.40±14.10	87.20±9.75	93.70±9.66	**0.007***	1.000	**0.043***	**0.009***
	10 min	66.40±11.48	67.60±12.07	72.40±11.00	0.125	0.595	0.137	1.000
Mean Arterial Pressure	2 min	94.90±12.03	99.00±8.77	112.30±8.68	**<0.0001***	1.000	**0.001***	**<0.001***
	10 min	80.10±10.28	79.90±12.09	85.10±9.66	0.090	0.334	0.107	1.000

*Mean±S.D. *:p value <0.05 (ANOVA, Bonferroni post hoc analysis). E- Esmolol, L- Lidocaine, C- Control. BIS- Bispectral index, BP- Blood pressure*

One patient in the esmolol group (3.3%) had hypotension, while no hypotension was recorded in the other groups (p = 0.125). No patients in any of the three groups had bradycardia. Three patients in the esmolol group (10%) and one patient in the lidocaine group (3.3%) had apnoea, while there was no incidence of apnoea in the control group (p = 0.356).

DISCUSSION

This study on the effects of esmolol and lidocaine on bispectral index (BIS) during propofol-fentanyl induction showed that the time to achieve induction (BIS of 50) and the dose of propofol required for induction were significantly reduced in the esmolol group compared to the control group. Though the time to induction and propofol dose in the lidocaine group were also reduced compared to the control group, this finding was not statistically significant.

In this study, the induction time with BIS-guided propofol administration in the control group (184.20±23.16 s) was longer than the time described in a different study when loss of verbal contact was employed (103.5±25.2 s – control group) [14]. This observation was corroborated by Saini et al. [15], who found that the time to reach BIS 50 (227.97±58.77 s) was significantly longer than the clinical end-points of induction (loss of palpebral reflex and loss of verbal command; 156.71±33.88 s and 155.06±32.57 s, respectively). This difference could be a result of the natural delay in the processing of EEG waves by the BIS monitor. Since the administration of propofol is guided by the BIS value, an intrinsic delay in the monitor will result in a longer duration of administration of the agent while waiting for the target value to be attained. According to the manufacturer, the BIS has a processing time delay of 5-10 s. However, Ferreira et al. [16] showed that the difference between the predicted and the observed BIS was ≥ 30 seconds; this shows that the delay in BIS processing may be much longer than what has been stated by the manufacturer.

This study demonstrated a 26% reduction (p<0.001) in the induction dose of propofol in the esmolol group compared to the saline group. Although there was a 13.4% reduction in the dose of propofol consumed in the lidocaine group, this was not statistically significant (p = 0.082). The impact of esmolol in reducing the induction dose of propofol has been supported by a study by Wilson et al. [17]. Currently, the mechanism by which esmolol decreases propofol requirement is unknown. It may do this by inhibiting central beta-adrenoceptors [18].

This present study agrees with the earlier findings of Stoneham et al. [19] that intravenous lidocaine had no effect on the induction dose of propofol (p = 0.082). Though it had a sedative effect, as reflected by a significantly lower BIS value before propofol administration, this did not translate to a significant reduction in the induction dose of propofol. However, Hans et al. [2], demonstrated a reduction in the requirements of propofol after surgical stimulation but not prior to any stimulation. The authors thus suggested that the antinociceptive action of lidocaine may be more at play than a pure hypnotic effect.

Administration of the study drugs resulted in a significantly lower BIS value before intubation in the lidocaine group than in the esmolol and control groups (96.30±1.49, 90±3.74 and 97.40±1.07, respectively; p <0.001). Similar findings were found by Kim et al. [3]. This suggests that systemic lidocaine had some hypnotic effect before any nociceptive stimulation.

In contrast, esmolol did not result in a significant change in BIS values before intubation. The study of Menigaux et al. [4] also concluded that the addition of esmolol to general anaesthesia with propofol did not affect BIS before intubation but attenuated BIS responses after intubation. Esmolol is thought to act centrally by blocking the beta receptor, preventing the sympathetic system's stimulating effect. Since there was no stimulation of the sympathetic system prior to endotracheal intubation, esmolol's effect on BIS was most likely not noticeable until after intubation. During the post-intubation period of this index study, the esmolol group had significantly lower BIS values than the lidocaine and control groups.

Although esmolol resulted in a 14.2% drop in the heart rate following its administration, this drop was transient and insignificant. Both the esmolol and lidocaine groups effectively prevented the increase in pulse rate associated with the autonomic response to laryngoscopy. Other studies have also reported the effectiveness of esmolol and lidocaine in attenuating the stress response due to laryngoscopy and intubation [7,12]. This may be because esmolol is a beta blocker that acts by blocking the sympathetic activity following

laryngoscopy and intubation, while lidocaine is known to blunt laryngeal reflexes, hence reducing the stimulatory effect of intubation.

Esmolol and lidocaine administration resulted in significantly lower SBP, DBP, and MAP values at two minutes post-intubation. The transient effect of esmolol on BP is probably because it is an ultra-short-acting, beta-one selective adrenergic receptor blocker with a peak onset of two minutes and a duration of action of about ten minutes. It has no alpha-adrenergic blocking effect required to suppress the sympathetic and sympathoadrenal activation accompanying tracheal intubation. Ambasta et al. [11] showed that labetalol with both beta and alpha-adrenergic blocking activity is more effective than esmolol in attenuating the sympathomimetic response to laryngoscopy and intubation. In our study, we chose to study esmolol instead of labetalol because of its safety profile, as the ultra-short duration of action also limited the duration of any side effects that may occur.

Lidocaine has a peak onset of two minutes, but the mechanism by which it affects haemodynamic parameters during pressor response is not yet understood. However, it is known to act by blocking sodium channels and thus decreasing the heart's contraction rate, causing direct cardiac depression and some peripheral vasodilation. In contrast to this present study, Jain and Vats [12], who used higher doses of esmolol and lidocaine, demonstrated that their effect on the SBP, DBP, and MAP was sustained up to the fifth minute in both groups.

Three patients in the esmolol group and one patient in the lidocaine group had apnoea, which was not statistically significant (p= 0.356). Propofol, on its own, causes apnoea with an incidence of 20-30% in younger patients and as high as 78-100% in the elderly, with apnoea defined as cessation of breath for greater than 30 to 40 seconds. The overall incidence of apnoea of 4.4% in this current study is much less despite using a cut-off time of ten seconds for defining apnoea. It is not yet known if either esmolol or lidocaine affects the incidence of apnoea associated with the use of propofol. However, Erb et al. [20] reported a significant reduction in the duration of central apnoea when lidocaine was given two minutes prior to inhalational induction with sevoflurane, while Hoiland et al. [21] reported an increase in the duration of apnoea break-point in elite breath-hold divers after beta-1 blockade with esmolol.

CONCLUSION

Intravenous esmolol 0.5 mg/kg given prior to laryngoscopy was more effective than intravenous lidocaine 1.5 mg/kg in reducing propofol's induction dose and time. Esmolol also prevented increases in BIS better than lidocaine following laryngoscopy and endotracheal intubation. Both esmolol and lidocaine at these doses were equally effective in attenuating the haemodynamic changes associated with pressor response to laryngoscopy and endotracheal intubation in patients induced with propofol/fentanyl.

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