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Anesthesiology

EFFECT OF ESMOLOL ON THE INDUCTION DOSE OF PROPOFOL

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ABSTRACT Induction, laryngoscopy and endotracheal intubation are an integral part of general anaesthesia. It leads to cardiovascular stress response. To avoid the rise in heart rate and mean blood pressure large doses of propofol during induction, are required to be given which are associated with complications. To prevent these complications various drugs like midazolam, dexmedetomidine, opioids are given along with propofol, which is supposed to decrease the total dose of propofol needed for induction. Esmolol which is β1-adrenergic receptor antagonist is known to decrease the rise in heart rate and mean blood pressure. This prospective randomised double blind study was planned to compare the effect of esmolol on induction dose of propofol on the patients undergoing surgeries. A total of 100 eligible patients were divided randomly into two groups, Group P (Propofol n=50), Group E (Esmolol n=50). Results showed that esmolol was able to reduce the total induction dose of propofol by 18.5%.

KEYWORDS : Induction, Hemodynamic response, Mean blood pressure, Propofol, Esmolol.

INTRODUCTION

Induction of anaesthesia literally means "creating hypnosis" which is brought about by various intravenous (IV) and inhalational agents. The IV agents are faster, smoother and short acting as compared to inhalation agents. The ideal IV anaesthesia agents should be haemodynamically stable, have a rapid and smooth onset of action and recovery, with no active metabolites, and good analgesic and amnesic properties. They should also have minimal effect on cardiovascular, respiratory and central nervous system.[1] Intravenous anaesthetic agents include barbiturates, benzodiazepines, ketamine, etomidate and propofol. Propofol is most popularly used IV induction agent because of its rapid, short duration of action and clear-headed recovery. Induction, laryngoscopy and intubation cause a stressful response leading to rise in the heart rate and blood pressure for which large induction doses of propofol are given.[2] These large dose can lead to cardiovascular depression, respiratory depression and delay in post-operative recovery and discharge.[3] Therefore, various drugs (e.g midazolam,dexmedetomidine, ketamine, opioids) have been used as premedication or co-induction agents along with propofol to reduce the total dose of propofol.[4]

Esmolol which is an ultra-short acting, cardioselective β1-adrenergic receptor antagonisthas shown to blunt the cardiovascular stress response of laryngoscopy and intubation by preventing the rise in heart rate and blood pressure and maintaining hemodynamic stability.[5-6] This effect is seen because of decrease in cardiac output which is as a result of reduction in stroke volume and heart rate.[7-8]

We propose to study the effect of esmolol on induction dose of propofol on the patients undergoing general anaesthesia for surgeries.

MATERIALS AND METHODS

This double blinded randomized clinical study was conducted at a tertiary care centre over a period of six months after obtaining approval from the institutional ethical review committee (ERC). Written informed consent was obtained from each patient after explaining about the technique of anaesthesia and surgery. The inclusion criteria included, patients belonging to American Society of Anaesthesiologist (ASA) physical status I and II, aged 18 to 65 years of either sex, undergoing routine surgeries requiring general anaesthesia. Exclusion criteria included patients with ischemic heart disease, heart blocks, hypertension, bradycardia, hypotension (Systolic blood pressure less than 90 mmHg), patients on beta antagonist therapy and sedatives/anxiolytics. Patients with body mass index (BMI) of more than 30, pregnancy, patients allergic to propofol and esmolol, having psychiatric and neurological problems and emergency surgeries were also excluded.

The patients were randomly allocated using computer generated random number tables into two groups, Propofol group (P) and Esmolol group (E). Hundred patients were included in the study and were randomised equally into respective groups on the day of surgery. Blinding was done by preparing equal volume of esmolol and normal saline in 10 ml syringe by an anaesthesiologist not involved in data collection. Both the patient and anaesthologists were blinded. On arrival in operation theatre (OT) standard monitors were attached [noninvasive blood pressure (NIBP), pulse-oximeter (SpO2), electrocardiography (ECG), end tidal carbon dioxide ($ETCO_2$)] and baseline readings were noted. Patients in both the groups were not pre-medicated with any drugs and before administration of propofol each patient was asked to open the eyes and start counting. During preoxygenation, patients in Group (P) received 10 ml of normal saline over 60 seconds. After two minutes propofol injection was given at the rate of 10 mg every five seconds until the patient stopped counting and did not count further even after being reminded to continue counting. Patients in Group (E) during preoxygenation received 1mg/kg of esmolol diluted in 10 ml over 60 seconds followed by injection propofol at the same rate as in GP (P). After the patient stopped counting there shoulder were prodded and in case of movement, additional boluses of 10 mg of propofol was given until there was no response. The observer's assessment of alertness/sedation (OAA/S) score was used to assess the sedation/alertness, which has score from 1 to 5.[9] OAA/S score of 1 is when patient does not respond to mild prodding or shaking, score of 2 is when patient responds to mild prodding or shaking, score of 3 is when patient responds only after name is called loudly and or repeatedly, score of 4 is when patient has a lethargic respond to name spoken in normal tone and score of 5 is when patient readily responds to name spoken in normal tone. OAA/S score of 2 was taken as the end point of study.

Total dose of propofol in both the groups were noted. Heart rate and mean arterial pressure (MAP) were recorded at five minutes (B5) and one-minute (B1) pre-induction and post-induction same parameters were recorded at one (A1) minute and five minutes (A5) in both the groups respectively.

Primary outcome measured was propofol dose per kilogram of body weight in both the groups required to achieve (OAA/S) of 2. Secondary outcomes were the change in heart rate and mean blood pressure in both the groups.

Results:

The study included 100 patients who completed the study and were divided equally into the two groups. [Figure1]

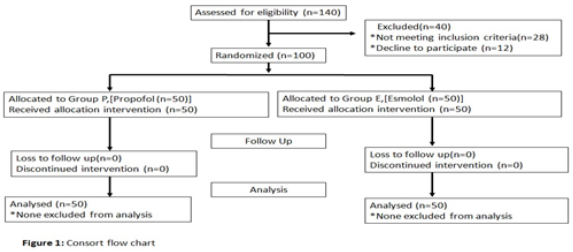


Figure 1: Consort flow chart

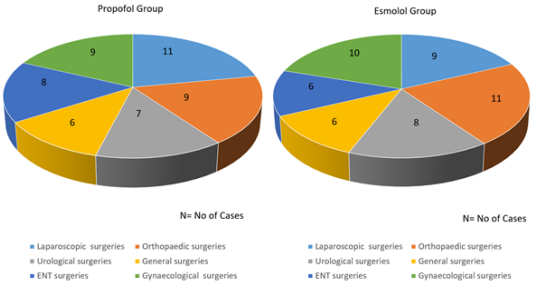
Demographic characteristics were comparable within the groups as being expressed in [Table1] and the type of surgeries included in both the groups have been expressed in the pie chart showing distribution. [Figure 2]

Table 1: Demographic characteristics

Parameter	GroupP n=50 (Propofol)	Group E n=50 (Esmolol)	P value
Age(year)	40.19± 15.33	40.54±15.23	0.90
Weight (Kg)	54.60±10.32	54.44±10	0.92
±Sex M/F	23/27	28/22	-
±ASA	29/21	27/23	-
Duration of surgery	85.23±34.23	86.91±34.89	0.82
Induction dose of propofol (mg/kg)	2.34 ± 0.20	1.91 ± 0.15	0.01

P value< 0.05 is considered significant. ± Values expressed as proportion.

Figure 2: Shows surgery wise distribution between the two groups.



In both the groups' heart rate before induction was comparable. One minute after induction, the mean decrease in heart rate was ten in Group E, whereas it increased by three in Group P.

The heart rate when was compared between the two groups showed significant results when measured one minute before the induction and henceforth at one minute and five minutes after induction. This reduction could be attributed to the use of the esmolol in the Group E which due to its beta blocker activity must have resulted in the decrease in the heart rate and the effect lasted for the duration of its half-life. [Table 2]

Table 2: Heart Rate comparison between the two groups.

Heart rate (HR) (beats per minutes)	Group P N=50	Group E N=50	P value
B5(Five minutes before induction)	76.8 ± 7.62	73.68 ± 6.89	0.33
B1 (One minute before induction)	79.21 ± 7.29	63.98 ± 6.97	0.01
A1 (One minute after induction)	83.48 ± 5.88	65.20 ± 5.75	0.01
A5 (Five minutes after induction)	82.82 ± 5.95	66.80 ± 6.32	0.01

Mean arterial pressure when compared between the groups showed significant results one minute before induction and followed by one minute and five minutes after the induction. This effect is evident in the Group E (Esmolol group) primarily owing to its beta blocker activities causing decrease in heart rate and reduction in the stroke volume which decreases the stress response. [Table 3]

Table 3: Mean Arterial Pressure (MAP) comparison between the groups

Mean Arterial Blood Pressure (mm hg)	Group P N=50	Group E N=50	P value
B5(Five minutes before induction)	86.44 ± 6.33	85.86 ± 5.77	0.63
B1(One minute before induction)	85.5 ± 6.37	79.58 ± 6.39	0.01
A1 (One minute after induction)	68.56 ± 5.1	63.7 ± 4.25	0.01
A5 (Five minutes after induction)	63.26 ± 4.89	60.18 ± 3.99	0.01

DISCUSSION

Propofol as compared to other intravenous induction agents (thiopental and methohexital) has faster induction, less nausea and vomiting, less hiccups, minimal excitatory effects, and rapid and clear headed recovery[10] The induction dose of propofol depends upon various factors which include age of patient, physical status, lean body mass, cardiac output, protein binding and anxiety.[11-14] Other factors include co-administration of other drugs, rate of injection, extent of surgical stimulus and use of premedication.[15-16] The normal induction dose of propofol ranges from 2 to 2.5 mg/kg in un-premedicated young healthy patients.[17] The anaesthetic requirement varies from patient to patient and depends upon various factors. Factors which increase the dose of anaesthetic drugs are hyperthermia, hypernatremia, acute cocaine abuse, chronic alcohol abuse, and infant's up to six months whereas hyponatremia, hypothermia, elderly, acute alcohol intoxication, pregnancy, anaemia, and hypoxemia lead to decrease in anaesthetic requirement.[18] In our study esmolol caused reduction in the induction dose of propofol by 18.5% whereas Johansen et al and Wilsonet al had shown the reduction in the induction dose of propofol by 26% and 25% respectively.[19-20]The most likely reason for this observation might be exclusion of the nitrous oxide, morphine and opioids during the induction which has been used by the many authors.[19] No major side effects of esmolol were seen in our study except transient bradycardia in two patients which recovered itself, which has also been documented by Kovac et al.[21] The esmolol dose used in our study is similar to miller et al, who had demonstrated decrease in cardiovascular stress response during laryngoscopy, intubation, and electroconvulsive therapy (ECT).[22] Esmolol as compared to midazolam,dexmedetomidine and opioids has a rapid peak effect at 1-2 minutes as opposed to others, which have peak effect at 3-5 minutes, therefore enabling esmolol as an ideal adjuvant to be used with propofol to innate timely induction dose with precision.[23] The exact mechanism of action of esmolol at the cellular level in reducing the induction dose of propofol has been studied by many and but still remains elusive. Meningaux et al had found that esmolol anaesthetic sparing effect was only seen when it was used as an adjuvant. [24] Other mechanism involved could be blockage of stress response to noxious stimulus and increases in the antinociceptive part of anaesthesia by esmolol.[25-26]The decrease in heart rate and MAP seen in our study was probably due to esmolol action on beta one receptors of sympathetic nervous system (SNS) found in heart and blood vessels. Blockade of beta one receptors leads to reduction in heart rate and stroke volume. Esmolol also prevents the action of epinephrine and nor-epinephrine, thereby preventing the stress response of laryngoscopy and intubation.[2] Esmolol in addition to reducing the perioperative anaesthetic requirement, also has been shown in decreasing the perioperative opioids requirement and the incidence of nausea and vomiting.[26-27]

The strength of our study was that, it was a double blind randomized study and the observer bias was eliminated.The limitation of the study was that the cardiac output and plasma concentration of propofol were not measured directly. Therefore, it is recommended that clinical trial involving a large number of patients should be done with direct measurement of cardiac output and serum propofol level.

To conclude, pre induction dose of Esmolol as an adjuvant is effective in reducing the induction dose of propofol.

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