Clinical Investigation

Influence of esmolol on requirement of inhalational agent using entropy and assessment of its effect on immediate postoperative pain score

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ABSTRACT

Background and Context: Beta-blockers have been used for attenuation of stress response, decreasing anaesthetic requirement and augmentation of the effect of opioids during general anaesthesia. **Aims and Objectives:** The present study aims to evaluate the influence of esmolol on the requirement of an inhalational agent while monitoring the depth of anaesthesia by entropy and also its effect on immediate postoperative pain score. **Methods:** Fifty American Society of Anaesthesiologists (ASA) I and II patients, between 25 and 65 years of age who underwent lower abdominal surgeries were randomly allocated to two groups: Group E and Group S of 25 patients each. Group E received esmolol infusion while Group S received the same volume of saline infusion. Demographic data, haemodynamics, amount of isoflurane used, end-tidal isoflurane concentration, postoperative pain score and total dose of morphine consumed in immediate postoperative period of 30 min were analyzed by using appropriate statistical tests. Value of $P<0.05$ was considered significant and $P<0.001$ as highly significant. **Results:** The two groups were comparable with respect to age, weight, ASA physical status, duration of surgery and amount of isoflurane used during anaesthesia. Assessment of postoperative pain was assessed by Visual Analogue Scale (VAS) which showed significant difference at 30 min. The total dose of morphine consumption was significantly less ($P<0.05$) in Group E for relief of postoperative pain. **Conclusions:** We conclude that in light of depth of anaesthesia monitor esmolol has no effect on requirement of isoflurane, but it decreases the postoperative pain as well as postoperative requirement of morphine without increasing the risk of awareness.

Key words: Beta-blockers, entropy, esmolol, isoflurane, opioids

INTRODUCTION

Beta-blockers such as esmolol have been used in anaesthesia practice to blunt the adrenergic response to various stimuli during perioperative periods such as in laryngoscopy, intubation, surgical stimulation and tracheal extubation.[1,2] The optimal approach to achieve the dual aims of obtunding the transient autonomic changes that occur in response to noxious surgical stimuli during surgery and facilitating prompt recovery after ambulatory anaesthesia, is still contentious. It is unclear whether these objectives are best achieved with opioids analgesics, sympatholytic drugs, sedative-hypnotics or other adjuvant drugs (e.g. adenosine, nicardipine).[3,4] β-blockers not only potentiate the hypnotic effects of anaesthesia but have also been demonstrated to reduce the dose requirement of intravenous and inhalational anaesthetics.[5]

Various clinical and physical modalities such as end-tidal anaesthetic concentration, minimum alveolar concentration (MAC), bi-spectral index system (BIS) and so on have been used to measure the depth of anaesthesia including. However, various studies showed discrepancies between clinical signs and even measurement of BIS has been questioned regarding its

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insensitivity to accurately measure anaesthetics like N_2O.[6] Entropy is the latest addition to these modalities which is a quantifiable measure of the sedative and hypnotic effects of anaesthetic drugs and is derived from electro-encephalography (EEG). It consists of two distinct variables of EEG, state entropy (SE) and response entropy (RE), which measures the cortical state as well as adequacy of analgesia.[7] This was a pioneer study which aimed at evaluating the influence of esmolol on requirement of inhalational agent while monitoring depth of anaesthesia by entropy in patients undergoing lower abdominal surgeries and also its effect on immediate postoperative pain score.

METHODS

After obtaining approval from the hospital ethics committee and informed consent from the patients, this study was conducted in 50 healthy ASA I and II patients of normal body mass index (BMI<25), age between 25 and 65 years, of either sex, undergoing lower abdominal surgeries. Patients with history of allergy to opioids or halogenated anaesthetics, or taking drugs and/or medications known to influence anaesthetic requirement including beta-blockers and opioids and pregnant patients and those with clinically significant cardiovascular, pulmonary, renal, and hepatic diseases were excluded from the study. Patients were randomly allocated to two groups depending on the infusion being used, esmolol (Group E) or saline (Group S), using concealed envelopes.

A routine pre-operative check-up of all patients was done one day prior to surgery and after explaining the anaesthetic procedure, informed consent was taken. No pre-anaesthetic medications were administered.

On arrival in the operating theatre 18G/20G intravenous cannula was placed and pre-loading done with 10 ml/kg of ringer lactate solution. After applying the standard monitoring which included continuous electrocardiography (ECG), heart rate (HR), non-invasive mean arterial pressure (MAP), pulse oximetry (SpO_2), inspired oxygen concentration (FiO_2) and M Entropy, every patient received a loading dose of randomly selected study drug infusion (0.5 mg/kg) over 5 min, 20 min before induction followed by a continuous infusion of the study drug at 0.5 mg/kg/min till the closure of skin incision. The study drugs were prepared by an anaesthesia technician who was given written instructions but was not aware about the design of the study. Induction was carried out by administering intravenous fentanyl (3.0 mcg/kg) and propofol (1.25-2.0 mg/kg) which was titrated to bring entropy between 40 and 60 and muscle relaxation was achieved with Atracurium (0.5 mg/kg). All the patients were hand-ventilated with oxygen in air through face mask with fresh gas flow of 4 liters/min and keeping the inspiratory fraction of oxygen (FiO_2) at 0.4. After adequate relaxation, laryngoscopy with Macintosh laryngoscope and subsequent intubation with portex PVC cuffed endotracheal tube of appropriate size was carried out in all the patients. The fresh gas flow was kept at 4 liters per min keeping the fractional inspired oxygen concentration at 0.4 for 10 min from the start of ventilation. After 10 min fresh gas flow was reduced to 1 liter per min, again keeping the FiO_2 0.4. The percentage (%) volume dial of isoflurane was set and changed to target both the RE and SE of the entropy monitor between 40 and 60. Controlled ventilation was achieved using tidal volume of 10 ml/kg and ventilatory rate was adjusted to keep $PaCo_2$ at 30–40 mm/Hg. Relaxation was maintained by bolus doses of Atracurium (0.15 mg/kg) as and when required. Intraoperative analgesia was maintained by bolus doses of fentanyl (1.0 mcg/kg) every 60 min.

Baseline readings of HR, ECG, MAP, End tidal carbon di-oxide ($EtCO_2$), pulse oximetry (SpO_2) and entropy were noted just prior to induction and thereafter at 1-min intervals for the first 5 min and at 5-min intervals starting from induction till extubation although all these parameters were monitored continuously. Peak airway pressures were monitored continuously during the operation and were always kept below 30 cm H_2O. The M-Entropy module provided with the Aestiva Datex Ohmeda anaesthesia machine was used as a depth of anaesthesia monitor. It has an EEG analyzer along with the spectral entropy module, combining both frequency and time domain approaches; in this module the speed of processing information is quite optimum and the basis of the algorithm is time frequency-balanced spectral entropy, which has the specific advantage that contributions to entropy from any particular frequency range can be easily separated. Isotec 5 vaporizer was used as vaporizer outside the circuit and its dial settings were changed to target the entropy readings of both RE and SE between 45 and 55. Dial setting was recorded at the start and at all the times when it was changed from the initial setting. The absolute value of MAC delivered to each patient was calculated every 3 min and noted and was compared later between the two groups. Consumption of isoflurane was calculated by formula:[8,9]

Consumption=CFTM/d 2412
Where C=agent dial setting (%)
F=fresh gas flow (liters/min)
T=time (min)
M=molecular weight
D=density of liquid agent (g/ml)

Vaporizer was switched off at the time of closure of skin and maintaining the fresh gas flow at 1.5 litre/min. Patients were extubated after administration of injection reversal and establishment of spontaneous rhythmic breathing. The patients were transferred to postoperative recovery ward and observed till fully awake. All the patients were followed up in the postoperative room for 30 min to assess visual analog scale for pain and managed with morphine boluses. The patients were examined after 24 h and were also asked about any kind of awareness during the peri-operative period.

All separate values were calculated as means±standard deviation (SD). Independent continuous data was analyzed by paired *t*-test, Wilcoxon signed Rank test and Mann Whitney test. Independent categorical data was analyzed by unpaired student's *t*-test. Accepting one-tailed α error of 5%; a sample size of 21 patients was calculated to achieve a power of 84.3% with a significant difference in absolute isoflurane requirement between the two groups to keep the entropy values between 40 and 60 during the peri-operative period. Value of $P>0.05$ was considered statistically significant and $P<0.001$ as highly significant.

RESULTS AND OBSERVATIONS

The demographic variables such as age, body weight, ASA physical status, duration of surgery and total amount of isoflurane used was comparable in both the groups and non-significant on statistical analysis ($P>0.05$) [Table 1].

Table 1: Demographic characteristics of patients in Group E and Group S

Demographic data	Group E (*n*=25)	Group S (*n*=25)	*P*
Age (in years) (mean±SD)	46.68±7.809	44.40±8.554	0.562
Body weight (in kg) (mean±SD)	63.62±8.997	66.97±9.386	0.873
ASA physical status (I/II)	15:10	12:13	–
Total duration of surgeries (min)	147.00±37.444	143.33±32.693	0.717
Total isoflurane used (ml)	24.399±8.573	22.325±7.967	0.385

$P<0.05$ represents significant changes; $P<0.001$ represents highly significant changes

End-tidal isoflurane concentration measurement was monitored continuously and was recorded every 5 min and the averages were taken at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120 and 140 min. There was significant difference in the end-tidal isoflurane concentration between the two groups at the 30-min interval ($P=0.047$) while at all other time intervals there were no significant difference between the end-tidal isoflurane concentrations [Figure 1].

Though the heart rate was monitored continuously and recorded at 5-min intervals, for the ease of comparison the average of the readings were taken at 10-min intervals till 140 min. There was a significant difference in the heart rate between both the groups at 60, 75, 90, and 105 min ($P<0.05$) [Figure 2].

Mean arterial blood pressure was also monitored continuously and recorded at 5-min intervals. For comparison of the blood pressures, the average of the readings was taken at 0, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120 and 140 min [Figure 3]. There were statistically significant changes ($P<0.05$) between the two groups at 60, 75 and 90-min intervals, rest of the time the changes in the two groups were proportional ($P>0.05$).

Minimum alveolar concentration was checked continuously starting at 5 min from induction and was recorded at 5-min intervals. Significant reduction in MAC was observed in Group E as compared to Group S at 30 ($P=0.038$), 40 ($P=0.011$) and 105 ($P=0.043$)-min intervals [Figure 4]. At all other time intervals there was no significant difference in MAC between the groups ($P>0.05$).

Pain was assessed in all the patients when they reached the postoperative room after extubation. VAS0 being the pain score at the time when they reached the postoperative room and VAS5, 10, 15, 20, 25 and 30 being the pain scores at respective time intervals which revealed a statistically significant difference in the VAS score between the groups at 5 and 10-min intervals [Table 2]. Dose of morphine used at 5, 10, 15, 20, 25 and 30 min for pain relief was calculated for both the groups and compared. Similarly, there was a statistically significant difference in morphine consumption at 5, 10, 25 and 30-min intervals ($P<0.05$). Total dose of morphine used in 30 min was also significantly less in Group E as compared to Group S ($P<0.05$).

Table 2: Comparison of visual analogue score and dose of morphine in both the groups

Time	Group E	Group S	*P* value (Mann Whitney test)	Time	Group E	Group S	*P* value Wilcoxon signed Ranx test
5 min	0.48±1.122	2.04±1.428	0.000**	VAS 5	3.40±1.190	4.60±1.472	0.003*
10 min	1.44±1.530	2.88±0.600	0.000**	VAS 10	4.24±1.234	6.04±1.306	0.000**
15 min	1.20±1.500	1.32±1.520	0.780	VAS 15	4.16±0.987	4.52±1.005	0.207
20 min	1.08±1.470	0.84±1.375	0.554	VAS 20	4.28±0.843	4.36±0.638	0.707
25 min	0.96±1.428	2.04±1.428	0.010*	VAS 25	4.32±1.030	4.84±0.987	0.074
30 min	0.00±0.000	0.96±1.428	0.002*	VAS 30	3.92±0.277	4.00±0.866	0.662
Total dose of morphine used in 30 min	3.72±1.308	7.20±1.732	0.000**				

*P<0.05 represents significant changes; **P<0.001 represents highly significant changes

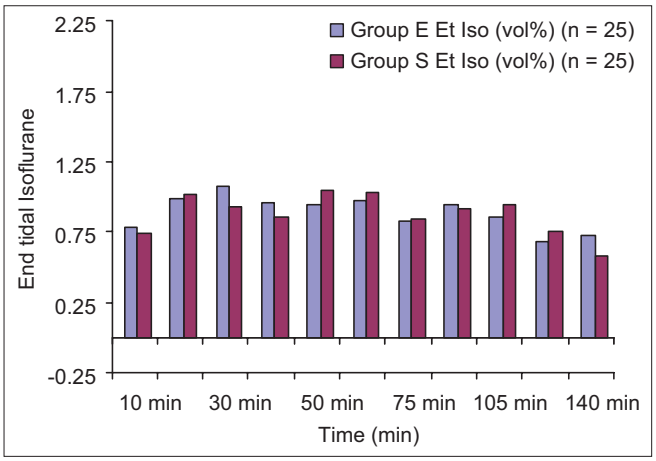

Figure 1: Comparison of end-tidal isoflurane concentration required to keep entropy values between 40 and 60 in patients of Group E and Group S

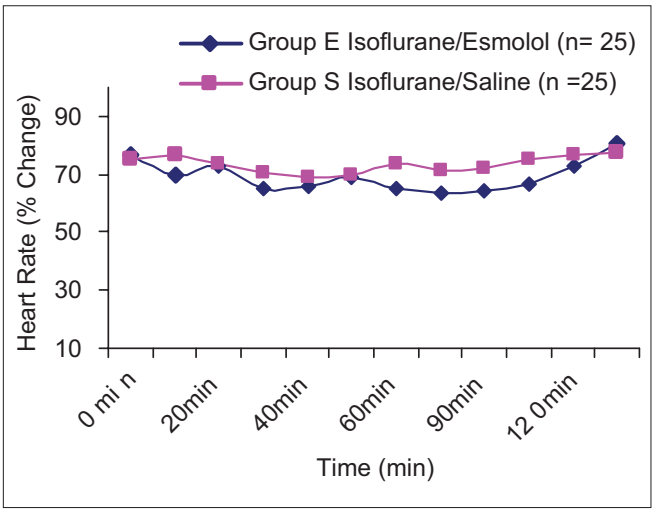

Figure 2: The heart rate pattern in patients of Group E and Group S

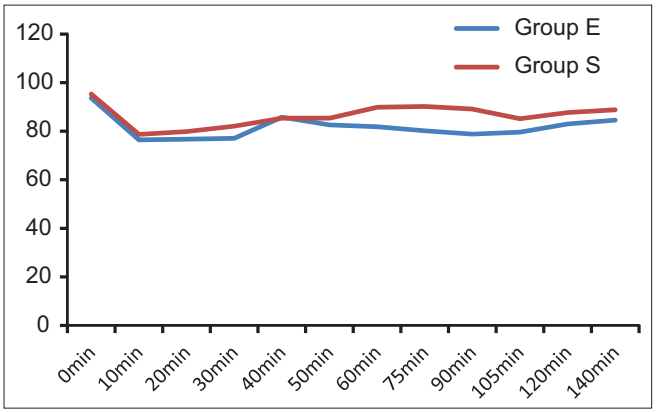

Figure 3: The mean arterial blood pressure comparison in patients of Group E and Group S

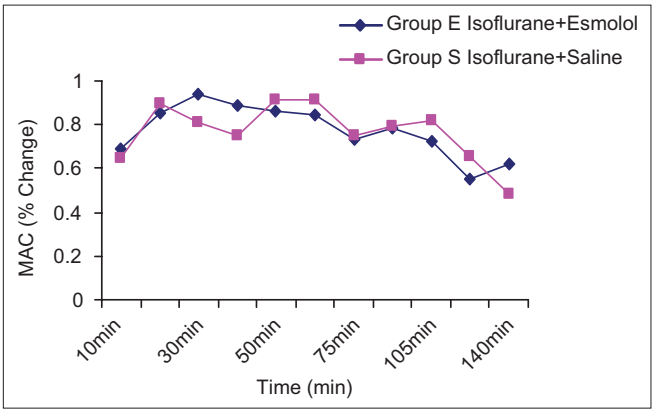

Figure 4: Changes in minimum alveolar concentration at different time intervals in both the groups

DISCUSSION

One of the main concerns with use of β-blockers for preventing peri-operative cardiac complications is the possibility of masking signs of light anaesthesia and the resultant risk of intra-operative awareness.[10] The central actions of β-blockers like decreased melatonin secretion, impaired memory and vigilance, anticonvulsant effect and anti-nociceptive effect are most possibly mediated through attenuation of excitatory neuronal responses in the cingulated gyrus or epileptiform responses in the limbic system.[11-14]

These clinical concerns with the use of β-blockers were, however, not completely addressed by the use of BIS which led to the designing of the present study. The lack of uniformity in predicting the depth of anaesthesia is a big limiting factor with use of

BIS which measures this entity based on probability and regression analysis. The other big limitation with the use of BIS as compared to entropy being the inability to measure other variables of different levels of 'inadequate anaesthesia' such as implicit memory, explicit memory, obeying commands during anaesthesia without recall, actual awareness and recall.[15,16]

The present study also aimed at examination of the efficacy of β-blockers in attenuating the incidence of intra-operative awareness. The actual present incidence of intra-operative awareness is approximately 0.15–0.17%.[17-19] Entropy has now been established to be as useful a monitor to assess the depth of anaesthesia as BIS. Though not recommended for routine monitoring, it has been suggested to be useful for research purposes.[16,20,21] Spectral Entropy (SpEn) was introduced and defined as Shannon Entropy, computed over the normalized power spectral density function.[22,23] It is an entropic measure which can be used as a measure of system complexity and is therefore included in this study. However, here the complexity of the system is understood as the number of different processes making up the time series rather than measure of complexity in the sense of regularity as understood in the case of previously described entropy rates measures.

Spectral Entropy (SpEn) is defined as

$$SpEn = -\sum_{i=1} p(\omega\, i) \ln p(\omega\, i)$$

Where $p(\omega\, i)$ is the probability density function (PDF) values at frequency ω i.

The PDF is obtained by normalization of the power spectral density function given by Fourier Transform.[8,22,23] M-Entropy TM is a measure that assesses the hypnotic component of anaesthesia and works as a part of the module-based monitoring system.

The present study had comparable demographic factors which provided us an ideal clinical situation to examine the fulfilment of our objectives. The effect of β-adrenergic blockers has been studied less extensively previously; however, the available literary evidence suggests that either acute or chronic administration of β-blockers has an inconclusive effect on the MAC of inhalational anaesthetics.[7,24-28] Throughout the study, intense monitoring was carried out and isoflurane was delivered to the patients by titrating and adjusting entropy values between 40 and 60. The total isoflurane consumption in Group E (24.399±8.573) and Group S (22.325±7.967) was comparable and statistically non-significant which establishes that esmolol did not influence the MAC values and requirement of isoflurane and coincides with observations of earlier studies.[7] Even the pharmacokinetic interaction of esmolol with opioids remains inconclusive though it is assumed that esmolol interacts with opioids to produce a dose-sparing effect. The most significant study in this direction involved a new highly cardio-selective β1-adrenergic antagonist landiolol hydrochloride which has a potency ratio (β1/β2) of 255 as compared to 33 and 0.68 of esmolol and propranolol respectively. The study established that the administration of landiolol neither affects the anti-nociceptive effect of isoflurane nor the effect on EEG by isoflurane.[29]

The non-measurement or lack of adequate monitoring using standard BIS or entropy, during usage of β-blockers while evaluating the effect on decreased requirement of inhalational or intravenous anaesthetics, has been the major difference between the present and the earlier studies. While evaluating the minimum dose requirement of isoflurane during maintenance of adequate depth of anaesthesia, monitoring with entropy and BIS is very essential so as to prevent any episode of intra-operative awareness which may not be possible with ordinary monitors displaying the routine parameters. No incidence of intra-operative awareness was reported by any patient from either of the groups.

Though a few studies have claimed that esmolol decreases the anaesthetic requirement the biggest limitation of these studies has been the measurement of depth of anaesthesia assessing only autonomic responses which are considered highly subjective and lack a true scientific base in the presence of modern monitoring gadgets.[30,31] The end-tidal isoflurane concentration and MAC values at 30 and 40 min [Figures 1 and 4] demonstrate a significant difference on comparison between the two groups. These observations have confirmed the fact that β-blockers do not exert any significant effect on consumption characteristics of isoflurane. It has also been successfully established that haemodynamic responses to noxious stimuli does not necessarily signify awareness. Further, the absence of stress response also does not ensure unconsciousness.[2,32,33]

Using paired *t*-test, it was observed that in patients

receiving esmolol (Group E), there was a statistically significant decrease in the heart rate for a larger part of the study period as compared to Group S patients. The mean arterial pressure also demonstrated similar significant trends in Group E as compared to Group S. These results are expectedly similar to most of the earlier studies which establishes the authenticity of the present study.[2,32-35]

The visual analogue scale was used for assessment of pain and comparison between the two groups was carried out using Wilcoxon signed Ranx test. The total dose consumption of morphine for relief of postoperative pain revealed a statistically significant difference at the 30-min interval ($P=0.000$) as indicated by the Mann Whitney test. The results of the present study are almost similar with the findings of the earlier studies in which the administration of esmolol exerted a dose-sparing effect on the consumption of opioids for relief of postoperative pain.[2,24,30,31] However, the most striking feature of all these studies is the failure of establishing conclusively the mechanism by which β-blockers help in reducing the dose of opioids for postoperative pain relief. The various mechanisms of opioids dose sparing with concomitant use of β-adrenergic antagonist have been proposed from time to time such as suppression of stress hormones and pro-inflammatory cytokines, alteration of hepatic drug metabolism, activation of G-coupled proteins in cell membrane, central analgesia and so on but nothing conclusive has been established as yet.[2,24,31]

CONCLUSION

We conclude that in light of depth of anaesthesia monitor, esmolol has no effect on the requirement of isoflurane but it decreases the postoperative pain as well as postoperative requirement of morphine without increasing the risk of awareness. Ours is a small study, and on the basis of this study alone, it is difficult to comment on awareness in a larger group. But, assuming that entropy is a good monitoring device to detect unconsciousness (as is claimed by the manufacturers and has been reported in a number of studies) we can conclude that esmolol does not affect the requirement of an inhalational agent. We also recommend larger studies to be done on this subject to draw some significant conclusions.

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