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RESEARCH ARTICLE
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DOSE SPARING OF INDUCTION DOSE OF PROPOFOL BY FENTANYL AND BUTORPHANOL: A COMPARISON BASED ON ENTROPY ANALYSIS

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Abstract

Introduction: Entropy monitoring is a method of assessing anaesthetic depth. There is abundant literature on the analgesic properties of butorphanol and fentanyl and its efficacy as an adjuvant to epidural and intra-thecal local anaesthetics, but not on dose sparing of induction dose.

Aim: The present study aims to compare the propofol requirement by fentanyl and butorphanol as pre-medication agent using entropy.

Methodology: The study was conducted on inpatients of hospitals attached to our institute for a duration of 18 months. This is a Prospective Randomized control trial that that included two groups, namely GROUP B included patients on Butorphanol [20 µg/kg] and GROUP F included patients on Fentanyl [2 µg/kg]. Seventy patients were randomly selected for each group, thus a total of 140 patients were included in the study.

Results: Response Entropy, State Entropy and Sedation score were comparable between group F and Group B without significant difference. The present study noted that Propofol requirement is comparable between group F and Group B without significant difference.

Discussion: Major drawbacks of anesthetic induction with propofol are a greater degree of cardiorespiratory depression as compared with other hypnotic agents and inadequate attenuation of the hypertensive response to intubation.

Conclusion: Butorphanol 20 µg/kg IV prior to the induction of anaesthesia reduces the induction dose of propofol, comparable to that of fentanyl 2 µg/kg IV and both the drugs are hemodynamic stable at induction and intubation.

Introduction

Propofol is one of a group of alkylphenols, that are oils at room temperature and insoluble in aqueous solution, but they are highly lipid soluble. Propofol is presumed to exert its sedative hypnotic effects through interaction with GABA, the principal inhibitory neurotransmitter in the CNS. When the GABA receptor is activated, transmembrane chloride conductance increases, resulting in hyperpolarization of post synaptic cell membrane and functional inhibition of post synaptic neuron. [1]

Entropy monitoring is a method of assessing anaesthetic depth. It was commercially developed by Datex-Ohmeda, now part of GE Healthcare. It relies on a method of assessing the degree of irregularity in electroencephalogram (EEG) signals. The founding principle behind this theory is that the irregularity within an EEG signal decreases with increasing brain levels of anaesthetic drugs. If we relate the irregularity to the entropy within the signal, then an entropy scale can be assigned. The signal is captured via a forehead mounted sensor, in a similar way employed by bispectral index (BIS). State of the brain is monitored by data acquisition of electroencephalograph (EEG) and frontal electromyograph (FEMG) signals. The spectral entropies, Response Entropy (RE) and State Entropy (SE), are processed EEG and FEMG variables. Response Entropy (RE) and State Entropy (SE) may be used as an aid in monitoring the effects of certain anesthetic agents, which may help the user to titrate anesthetic drugs according to the individual needs of adult patients. [2-4]

Fentanyl is a synthetic opioid, phenylpiperidine series acting on the *u* receptors. Fentanyl is approximately 100 times more potent than morphine. Peak analgesic effect after intravenous administration is being reached in about 5minutes, short acting [30-50min], elimination $t^{1/2}$~4hrs. Nausea, vomiting and itching can be observed after the administration of Fentanyl. [5]

Butorphanol is a synthetic opioid, morphinan series has mixed agonistic antagonistic properties. It is a *k* opioid receptor agonist and antagonist at *u* opioid receptor. The analgesic effect of 2-3 mg Butorphanol is approximately equal to 10mg of morphine. Plasma $t^{1/2}$~3hrs. The most prominent side effect is sedation, nausea and sweating. [6]

There is abundant literature on the analgesic properties of butorphanol and fentanyl and its efficacy as an adjuvant to epidural and intra-thecal local anaesthetics is well documented. However, few studies are present on the sparing effect of fentanyl and butorphanol on induction dose of propofol and regarding the effect of fentanyl and butorphanol on Entropy.

Many studies portend the use of Butorphanol and Fentanyl as pre-medication agents, but as there is no firm conclusion derived as yet, especially on dose sparing of induction dose of propofol by butorphanol and fentanyl and its effect on entropy. This study would help to throw some light in this regard. [7,8]

AIM: The present study aims to compare the propofol requirement by fentanyl and butorphanol as pre-medication agent using entropy. The present study compares the safety profile of the above agents.

MATERIALS AND METHODS

The study was conducted on inpatients of hospitals attached to our institute for a duration of May 2016 to November 2018, accounting to 18 months of the study duration. This is a Prospective Randomized control trial that that included two groups, namely GROUP B included patients on Butorphanol [20 µg/kg] and GROUP F included patients on Fentanyl [2 µg/kg]. Seventy patients were randomly selected for each group, thus a total of 140 patients were included in the study. This study included patients belonging to 18-65 years of age of either sex, ASA physical status I and II for surgeries under general anaesthesia and Patients who gave informed written consent. We excluded the patients refusing to participate in the study. The patients with history of Neurological, Respiratory, Cardiovascular and Hepatic disorder, BMI more than 30 and individuals with difficult airway, Allergy to the study drug, Patients on opioids, sedatives, anti-psychotics, anti-epileptics, Pregnant or lactating mothers and Alcoholics were excluded from the study.

Following approval of institutional ethical committee, 140 patients were taken up for the study. A routine pre anaesthetic checkup was done in the evening before the surgery. A detailed examination of the cardiovascular system, Respiratory system and Central nervous system & other systems,

examination of the spine was done. The routine investigations were done in all patients and written informed consent was obtained. All patients were kept nil per oral for 8 hours prior to surgery. All patients on arrival to the operation theatre, intra venous line was secured with 18G cannula and intra venous fluid was on flow. Pulse oximeter, Non-invasive blood pressure and ECG monitors, Entropy were connected. Base line Entropy values was recorded.

Patients were randomly allocated into two groups of 70 each using sealed envelope technique. Premedicated with Inj. Glycopyrrolate 0.2mg plus Group F: Inj.Fentanyl 2mcg/ kg and Group B: Inj.Butorphanol 20mcg/ kg. Study drug dose was calculated per kg body weight and diluted to 5ml with normal saline and given as pre-medication 5minute before the procedure. Entropy values was recorded @ 1 & 5 minutes after pre-medication. Sedation level was assessed by OAA/S scale @ 1 & 5 minute after pre-medication. Patient was pre-oxygenated with 100% oxygen for 3minutes prior to induction of anaesthesia.

Patients were induced with Inj. Propofol 30mg/10seconds and entropy values was recorded for 2 minutes after induction. Inj. Succinyl choline 2 mg/ kg was given. After adequate relaxation, endotracheal intubation was performed. Entropy values was recorded for 5 minutes after intubation. To ensure blinding, the parameters were recorded by anesthetist not involved in the study.

Statistical Methods: Descriptive and inferential statistical analysis had been carried out in the present study. Results on continuous measurements were presented on Mean ± SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. The assumptions on data such as,dependent variables should be normally distributed, the samples drawn from the population should be random, and the Cases of the samples should be independent Student t test (two tailed, independent) had been used to find the significance of study parameters on continuous scale between the two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test had been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. *Significant figures were divided into* significant (P value: $0.05<P<0.10$), moderately significant (P value: $0.01<P \leq 0.05$) and strongly significant (P value: $P \leq 0.01$). The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Results

The present study is a clinical randomized double blinded study with 140 patients randomly divided into two groups of 70 each, Group F receiving Fentanyl and Group B receiving Butorphanol. The entropy values and the OAA/S were recorded among the study population.

Response Entropy was comparable between group F and Group B without significant difference (Table 1 and Figure 1). State Entropy is comparable between group F and Group B without significant difference (Table 2 and Figure 2). Sedation score is comparable between group F and Group B without significant difference (Table 3). The present study noted that Propofol requirement is comparable between group F and Group B without significant difference (Figure 3). Propofol requirement in Group F & Group B was comparable between two groups without significant difference between the two groups (Table 4).

Table 1: Comparison of RE in two groups of patients studied

RE	Group F	Group B	Total	P value
Baseline	94.43±2.99	94.53±2.99	94.48±2.98	0.843
1 Minute after Premedication	94.39±3.01	94.09±2.94	94.24±2.97	0.552
5 Minute after premedication	83.24±2.94	83.31±3.03	82.78±3.02	0.889
At Induction	80.60±5.62	81.69±3.42	81.14±4.66	0.169
1 Minute after induction	60.46±6.16	59.49±6.10	59.97±6.13	0.350
2 Minute after induction	52.83±4.79	52.29±5.09	52.56±4.93	0.516
1 Minute after intubation	55.13±5.23	56.59±4.90	56.86±5.34	0.090
2 Minute after intubation	52.96±4.93	54.49±4.51	56.22±5.73	0.057

3 Minute after intubation	52.00±5.05	53.37±4.20	56.19±6.25	0.083
4 Minute after intubation	52.64±4.70	54.00±4.62	57.44±6.68	0.086
5 Minute after intubation	52.49±4.74	53.70±4.38	57.59±6.85	0.119

Figure 1: showing response entropy of two groups studied

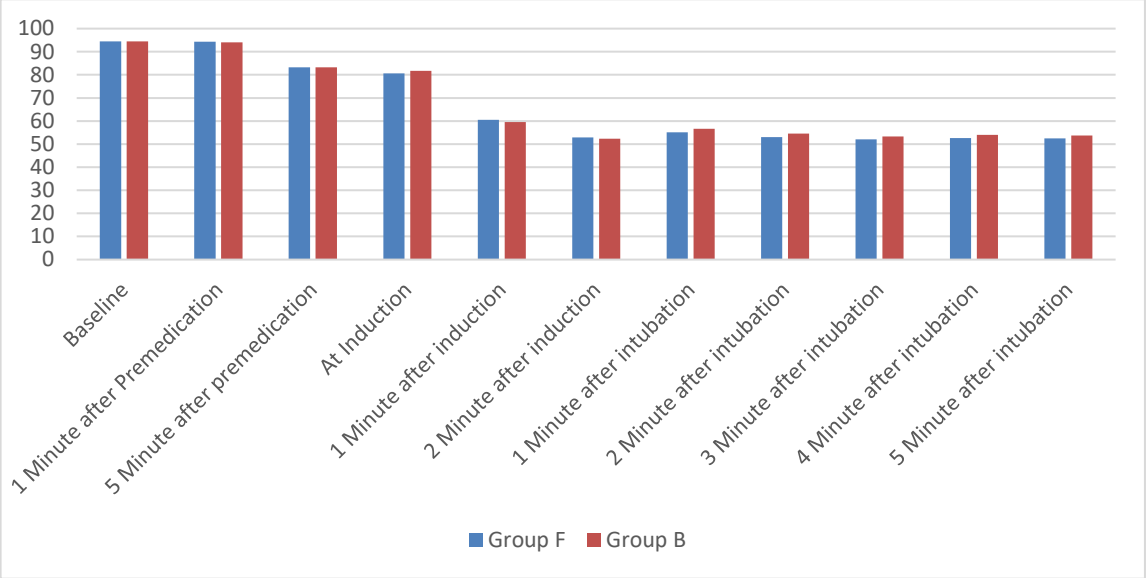

Table 2: Comparison of SE in two groups of patients studied

SE	Group F	Group B	Total	P value
Baseline	84.83±2.95	84.79±2.97	84.81±2.95	0.932
1 Minute after Premedication	84.66±3.01	84.51±3.08	84.59±3.03	0.782
5 Minute after premedication	74.07±3.08	74.30±2.77	74.69±2.98	0.643
At Induction	72.97±4.40	73.84±3.04	73.91±3.88	0.175
1 Minute after induction	55.47±5.85	53.7±6.34	54.59±6.14	0.088+
2 Minute after induction	50.94±4.82	49.94±5.25	49.94±5.12	0.242
1 Minute after intubation	51.16±4.94	52.06±3.67	52.11±4.44	0.223
2 Minute after intubation	50.36±4.94	51.03±3.58	52.19±4.68	0.359
3 Minute after intubation	50.44±4.84	51.67±3.73	52.56±4.8	0.094
4 Minute after intubation	50.41±4.84	51.8±4.27	53.11±5.29	0.073
5 Minute after intubation	50.39±4.85	51.11±4.08	53.25±5.31	0.343

Figure 2: showing Comparison of SE in two groups of patients studied

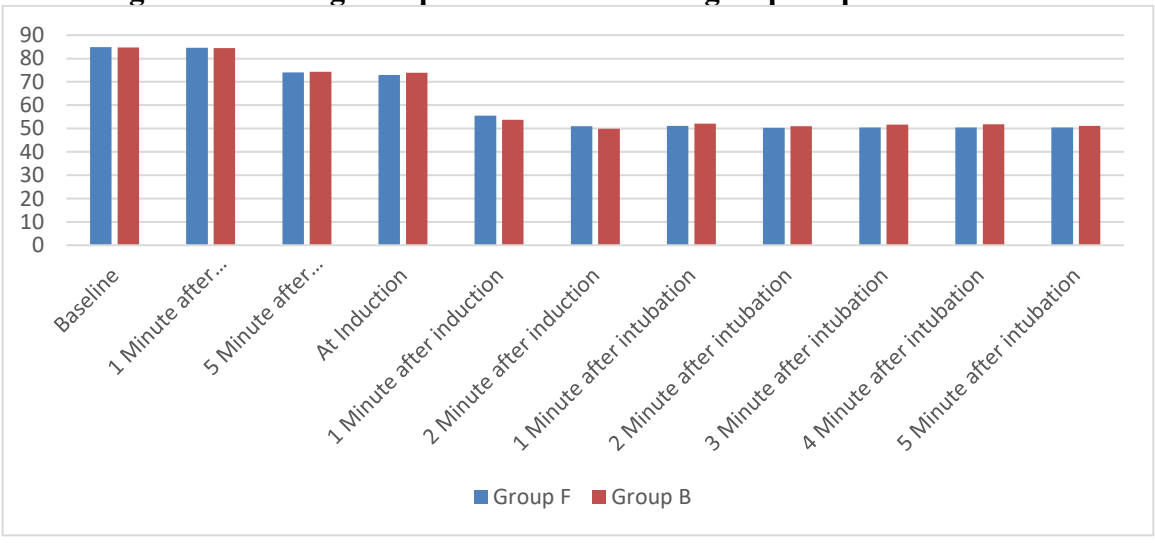

Table 3: Comparison of OAA/S in two groups of patients studied

OAA/S	Group F	Group B	Total	P value
Baseline	5.00±0.00	5.00±0.00	5.00±0.00	-
1 Minute after Premedication	4.94±0.23	4.93±0.26	4.94±0.25	0.733
5 Minute after premedication	4.40±0.55	4.31±0.53	4.36±0.54	0.347

Figure 3: Comparison of Propofol (mg) in two groups of patients studied

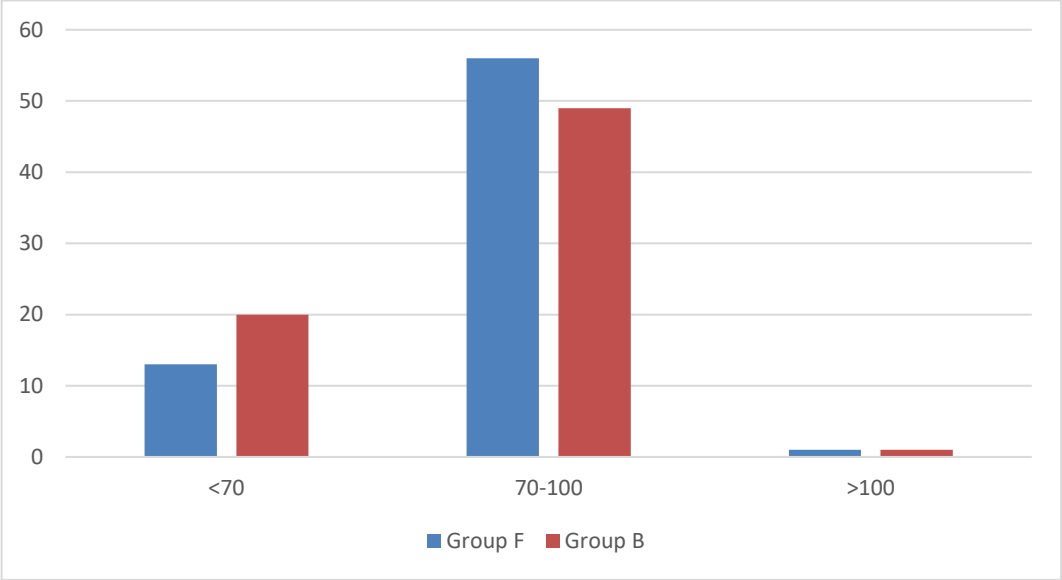

Table 4: Propofol requirement among the two groups

Propofol	Group F	Group B	Total	P value
Propofol mg/kg	1.272±0.133	1.238±0.122	1.26±0.10	0.117

Discussion

Among the various induction agents, propofol has become most popular agent in the last two decades for the induction of anesthesia. The recommended intravenous induction dose is 2.5 mg/kg, corresponding to the dose producing unconsciousness in 95% of the subjects. However, the major drawbacks of anesthetic induction with propofol are a greater degree of cardiorespiratory depression as compared with other hypnotic agents and inadequate attenuation of the hypertensive response to intubation. Propofol requirements for induction are reduced in the presence of an opioid. [1]

Fentanyl has been studied extensively and is added during induction of anesthesia to provide analgesia during surgical procedures and to decrease the hypertensive response to intubation. It is also known to potentiate the hypnotic effect of propofol. Butorphanol is a kappa-receptor agonist as well as a mu-receptor antagonist, resulting in analgesic and sedative properties without profound respiratory depression or euphoria. It was hypothesized that butorphanol, due to its sedative effects, would reduce the requirements of propofol at induction comparable to fentanyl. [7,9]

This study was done to compare the propofol induction dose with butorphanol and fentanyl pre-treatment, using entropy. Demographic data comparing Age, Sex, weight, height, BMI, ASA grade shows no statistically significant difference among two groups.

Clinical end point for induction of anaesthesia with propofol was considered as loss of response to verbal commands and entropy values was noted at that time. Average requirement of propofol was found to be 1.272 ± 0.133(mg/kg) in Group F and 1.238± 0.122(mg/kg) in Group B with P value of 0.117. The results of our study showed that the reduction in the induction dose of propofol with 20 µg/kg of butorphanol was comparable to fentanyl 2 µg/kg. The loss of response to verbal commands occurred at normal entropy values [40-60] in both fentanyl and butorphanol groups. Two studies in

dogs reported that butorphanol, along with other premedicants, significantly reduced the dose requirement of propofol at induction. [23, 24] In another study in cats, premedication with butorphanol or morphine, combined with acepromazine, significantly reduced the propofol dose for induction. [25]
Jasleen kaur et al[9] [2013] studied dose sparing of induction dose of propofol by fentanyl(2mcg/kg) and butorphanol(20mcg/kg and 40mcg/kg) on 120patients three groups of 40 each & the induction dose of propofol (mg/kg) was observed to be 1.1±0.50 in Group F, 1.05±0.35 in Group B 20 and 1.18±0.41 in Group B40. The results obtained in our study is in consistent with the previous study of Jasleen kaur et al where the requirement of propofol with butorphanol 20mcg/kg as pre-medicant is comparable to fentanyl 2mcg/kg.
In 2004, W.Riad et al [10] studied the effect of electroencephalographic entropy on propofol requirement and haemodynamic parameters during induction of anaesthesia in 72 elderly patients. Standard monitoring was performed for all patients together with entropy monitor. Total dose of propofol and the dose kg-1 were significantly reduced by 37.1% and 31.8%, respectively, in the entropy group (P value < 0.01)**.** The requirement of propofol in our study was found to be 1.272±0. 133(mg/kg) in Group F and 1.238± 0.122(mg/kg) in Group B. Considering 2mg/kg as the conventional dose, total dose of propofol was reduced by 36.4% in group F and 38.1% in group B. The results obtained in our study is in consistent with the previous study of W.Riad et al where there is reduction in the requirement of propofol by more than 30% by using simultaneous entropy monitoring and clinical end point and the requirement of propofol with butorphanol 20mcg/kg as pre-medicant is comparable to fentanyl 2mcg/kg.
In Jasleen kaur et al [9] [2013] study, Response entropy and State entropy was higher than 60 at induction in all three groups. But, in our study RE and SE at induction was between 50-60 in both fentanyl 2mcg/kg and butorphanol 20mcg/kg group. This is in contrast to the study of Jasleen kaur et al study who had obtained an entropy values of higher than 60 in fentanyl 2mcg/kg and butorphanol 20mcg/kg and butorphanol 40mcg/kg.
Depth of sedation and alertness was assessed using the responsiveness scores of the modified OAA/S. Butorphanol 20mcg/kg had lower sedation scores compared to fentanyl 2mcg/kg at 1minute and 5 minute after pre-medication but there was no statistically significant difference in sedation scores in the fentanyl and butorphanol group at doses 2mcg/kg and 20mcg/kg respectively. This difference could be explained due to the difference in the opioid receptor spectra. Butorphanol is a kappa-receptor partial agonist as well as a mu-receptor antagonist, whereas fentanyl is predominantly a mu-receptor agonist. Butorphanol is therefore associated with more sedation than fentanyl.
In **Jasleen kaur et al [9] [2013] study** higher sedation was observed in the butorphanol groups especially with 40mcg/kg [4.1+/-0.64] of butorphanol than 20mcg/kg of butorphanol [4.3+/-0.60] as compared with Group F [4.57+/-0.54]. Butorphanol at higher doses [40mcg/kg] increases the depth of sedation without much reduction in the consumption of propofol. So, at the dose used in our study [20mcg/kg butorphanol] sedation scores are similar to the previous study of Jasleen kaur et al without significant

Conclusion

Butorphanol 20 µg/kg IV prior to the induction of anaesthesia reduces the induction dose of propofol, comparable to that of fentanyl 2 µg/kg IV and both the drugs are hemodynamic stable at induction and intubation. Butorphanol due to its lack of euphoric effects may be useful for clinical populations prone to drug-seeking behavior.[21] Butorphanol is not a controlled substance, its use can reduce administrative liability for abuse and can lower the number of distribution records associated with Schedule II narcotics. It is also economical than fentanyl. So, Butorphanol 20mcg/kg is an acceptable alternative to fentanyl as an adjuvant to balanced general anaesthesia.

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