ORIGINAL ARTICLE

Dose sparing of induction dose of propofol by fentanyl and butorphanol: A comparison based on entropy analysis

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ABSTRACT

Background: The induction dose of propofol is reduced with concomitant use of opioids as a result of a possible synergistic action. **Aim and Objectives:** The present study compared the effect of fentanyl and two doses of butorphanol pre-treatment on the induction dose of propofol, with specific emphasis on entropy. **Methods:** Three groups of 40 patients each, of the American Society of Anaesthesiologistsphysical status I and II, were randomized to receive fentanyl 2 μg/kg (Group F), butorphanol 20 μg/kg (Group B 20) or 40 μg/kg (Group B 40) as pre-treatment. Five minutes later, the degree of sedation was assessed by the observer's assessment of alertness scale (OAA/S). Induction of anesthesia was done with propofol (30 mg/10 s) till the loss of response to verbal commands. Thereafter, rocuronium 1 mg/kg was administered and endotracheal intubation was performed 2 min later. OAA/S, propofol induction dose, heart rate, blood pressure, oxygen saturation and entropy (response and state) were compared in the three groups. **Statistical Analysis:** Data was analyzed using ANOVA test with *posthoc* significance, Kruskal–Wallis test, Chi-square test and Fischer exact test. A $P<0.05$ was considered as significant. **Results:** 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. Induction with propofol occurred at higher entropy values on pre-treatment with both fentanyl as well as butorphanol. Hemodynamic variables were comparable in all the three groups. **Conclusion:** Butorphanol 20 μg/kg and 40 μg/kg reduce the induction requirement of propofol, comparable to that of fentanyl 2 μg/kg, and confer hemodynamic stability at induction and intubation.

Key words: *Butorphanol, entropy, fentanyl, propofol*

INTRODUCTION

Among the various induction agents, propofol has become increasingly popular 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.[1] However, the major drawbacks of anesthetic induction with propofol are a greater degree of hypotension as compared with other hypnotic agents and inadequate attenuation of the hypertensive response to intubation.[2,3]

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Studies have demonstrated that the propofol requirements for induction are reduced in the presence of an opioid.[2,3] 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.[4,5] It is also known to potentiate the hypnotic effect of propofol.[3,6]

Butorphanol is a morphinan, chemically related to levorphanol, and has mixed agonist-antagonist properties.[7] It is a kappa-receptor agonist as well as a mu-receptor antagonist, resulting in analgesic and sedative properties without profound respiratory depression or euphoria.[4] The most prominent side-effect is sedation, a property that is generally quite useful in the perioperative period. There is abundant literature on the analgesic properties of butorphanol. Its efficacy as an adjuvant to intrathecal and epidural local anesthetics for intraoperative and post-operative use is well documented.[5,8] However, the sparing effect of butorphanol on induction

doses of propofol has not been evaluated in humans earlier. Entropy consists of two distinct variables of electroencephalography (EEG), state entropy (SE) and response entropy (RE).There is no literature regarding the effect of butorphanol on RE and SE.

It was hypothesised that butorphanol, due to its sedative effects, would reduce the requirements of propofol at induction comparable to fentanyl. The aim of this study was to compare the propofol induction dose with butorphanol and fentanyl pre-treatment, using clinical end-points and entropy, and to identify the optimal dose of butorphanol that would augment the hypnotic effect of propofol without undue adverse effects such as increased sedation and delayed post-operative recovery. The secondary outcome was to compare the hemodynamic changes during propofol induction with these drugs.

METHODS

A double-blind, prospective, randomized, comparative study was conducted on 120, American Society of Anaesthesiologistsphysical status I and II patients, aged between 18 years and 65 years, of either sex, undergoing elective surgery under general anesthesia. Approval for the study was obtained from the institute's ethical committee and written and informed consent was taken from the patients after explaining the nature of the study. Exclusion criteria included history of cardiac, cerebrovascular, respiratory, hepatic or renal disease, allergy to the study medications, risk of regurgitation, predicted difficult airway, obesity (Body mass index- (BMI) >30 kg/m^2) and pregnancy. Patients with history of alcohol or opioid abuse and on sedative, anti-convulsant, anti-psychotic and anti-hypertensive medications were not included in the study.

Patients were kept fasting for 8 h and were not administered any sedative pre-medication on the day of surgery. In the operating room, the patient was connected to the monitor with a DatexOhmeda 7100 workstation and an intravenous line was secured in a peripheral vein. The baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), respiratory rate (RR), oxygen saturation (SpO_2) and RE and SE were recorded. The patients were randomly allocated into three study groups of 40 patients each, using a sealed envelope technique. Group F patients received intravenous fentanyl 2 μg/kg, Group B 20 patients received butorphanol 20 μg/kg and Group B 40 patients received butorphanol 40 μg/kg. The drugs were prepared in the identical syringe and in equal volume by the technician, and the anesthesiologists were blinded to the drug.

The patient remained undisturbed for 5 min after administration of the study drug and thereafter, the sedation level was assessed using the observer's assessment of alertness scale (OAA/S)[9] and SE and RE were noted. Patients were observed for nausea, vomiting, pruritis, RR <8 min and SpO_2 <90%. Oxygen (O_2) supplementation through face mask was administered when SpO_2 was <90%. Intravenous lignocaine 40 mg with proximal venous occlusion was administered prior to administration of propofol to alleviate the pain. Anesthesia was then induced with propofol (30 mg/10 s) using a syringe pump till the loss of response to verbal commands and RE and SE were noted. The anesthesiologist who performed all the clinical observations was blinded to the study drug administered. Subsequent muscle relaxation was achieved with rocuronium 1 mg/kg. The patient's lungs were manually ventilated with 100% O_2 for 2 min before endotracheal intubation was performed. Following intubation, anesthesia was maintained with 1% isoflurane in oxygen: Nitrous oxide (35%:65%). No stimulus was given to the patient for 5 min post-intubation and RE and SE were noted at 1 min intervals. The HR, SBP, DBP and MAP were also recorded before administration of the study drugs, 5 min thereafter, at the time of induction, for 2 min post-induction and post-intubation for 5 min at 1 min intervals. We also observed the incidence of hypotension (fall in systolic blood pressure >30% from baseline). Hypotension was treated with rapid infusion of 200 ml aliquots of Ringer's Lactate (up to 1000 ml) until restoration of blood pressure to >70% of the baseline. Intravenous ephedrine 5 mg boluses would be administered if there was no response to fluid administration. Sustained hypertension was considered if systolic blood pressure remained >20% above baseline for 3 min post-intubation. It was treated with increase in isoflurane concentration at 0.5% increments. The study concluded 5 min after intubation. The remaining part of the anesthesia regimen was at the discretion of the attending anesthesiologist. All the patients were interviewed on the first post-operative day and asked for any post-operative recall of intraoperative events.

Statistical analysis

A pilot study was performed on 20 patients for the estimation of sample size. A difference in the propofol induction dose requirement of 0.15 mg/kg was considered as equivalent of the groups. With a true mean difference of 0.09 and standard deviation of 0.1, the estimated sample size with an alfa-error of 0.05 and power of 80% for equivalence of groups was 36 in each group. Forty patients were therefore recruited in each group.

Statistical analysis was performed using statistical product and service solutions (SPSS-version 13). Data are expressed

as mean with standard deviation for normally distributed continuous variables and median with inter quartile range for ordered categorical variables not distributed normally. Discrete data is expressed as frequency with percentage of total. Normal distribution was tested using the Kolmogorov–Smirnov test. Normally distributed continuous variables were compared using ANOVA with *posthoc* analysis using Bonferroni test. Kruskal–Wallis test was used to compare ordered categorical variables. Chi-square test and Fischer exact test were used to compare discrete variables between the groups. A $P<0.05$ was considered as a significant difference.

RESULTS

Demographic parameters of age, height, weight, BMI and gender were comparable in all the three groups [Table 1]. Baseline SpO_2 and RE and SE were also comparable. Five minutes after the administration of the study drug, a statistically significant difference in SpO_2 was observed between Group F and GroupB 20 ($P=0.027$). The mean value of OAA/S was 4.57±0.54, 4.30±0.60 and 4.10±0.64 in Group F, Group B20 and Group B40, respectively. There was a statistically significant difference in the OAA/S between Group F and Group B40, as Group B40 had a deeper sedation level ($P=0.003$). The propofol induction dose was comparable in all the three groups ($P=0.40$) [Figure 1]. All patients had clinical signs of induction at RE and SE higher than 60. MAP, RE and SE at induction were 82.50±4.53 and 76.07±3.97 in Group F, 85.80±9.04 and 78.02±9.01 in Group B20 and 84.60±7.35 and 77.87±7.09 in Group B40 [Figure 2 and 3].There was no statistically significant difference in the three groups ($P=0.085$, $P=0.396$). Changes in the entropy following induction and intubation were also similar in the three groups.

Changes in the HR and SBP are shown in Figure 4. Patients in all the three groups had a comparable increase in HR in the post-intubation period, which returned to baseline within 5 min. Post-induction hypotension was seen in six patients (15%) in Group F, eight patients (20%) in Group B20 and four patients (10%) in Group B40. This difference was not statistically significant ($P=0.456$). Only seven patients (17.5%) in Group F, six patients (15%) in Group B20 and 10 patients (25%) in Group B40 had an increase in SBP (>20% of the baseline) in the post-intubation period. This was also not statistically significant ($P=0.497$).

No patient complained of nausea or vomiting after administration of the study drugs. Only three

Table 1: Demographic data as mean±standard deviation

	Group F	Group B20	Group B40	*P* value
Age (year)	40.07±14.31	37.85±12.40	35.24±12.76	0.26
Height (m)	1.61±0.09	1.59±0.06	1.63±0.08	0.18
Weight (kg)	58.87±11.57	55.30±12.18	54.65±10.62	0.21
BMI	22.42±3.56	21.52±3.92	20.51±3.43	0.06
Gender (M/F)	25/15	21/19	23/17	0.51

BMI – Body mass index; M – Male; F – Female

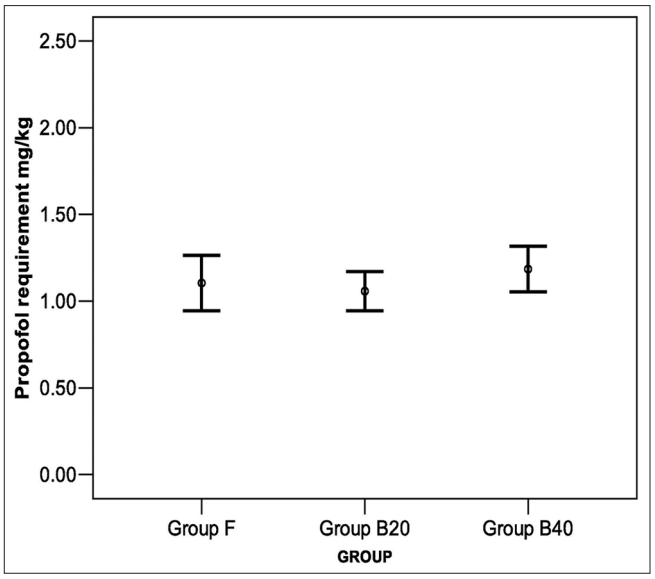

Figure 1: Comparison of propofol induction dose requirement in the three groups. No statistically significant difference in the three groups ($P=0.40$)

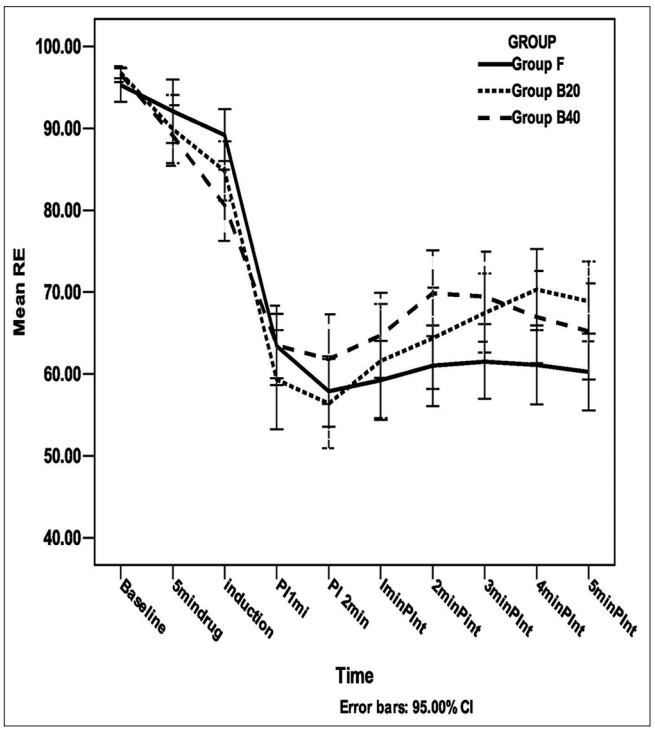

Figure 2: Comparison of response entropy in the three groups

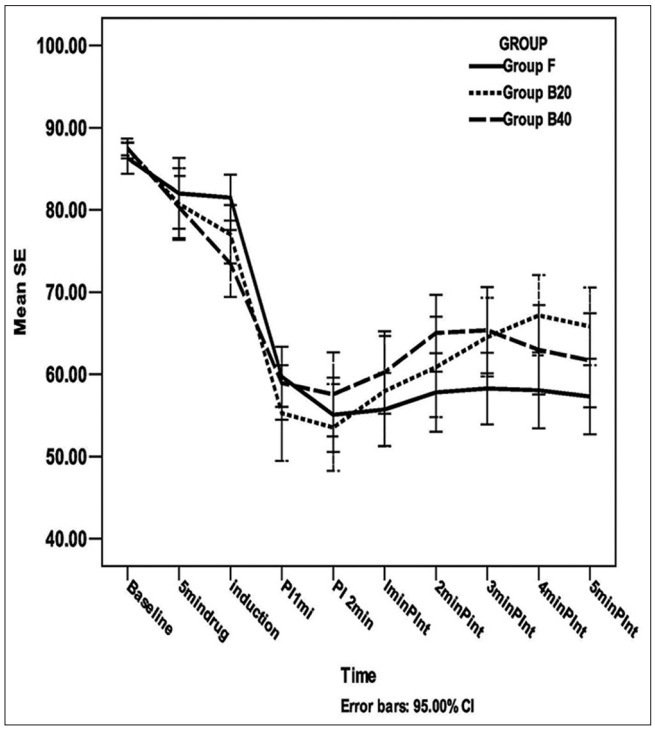

Figure 3: Comparison of state entropy in the three groups

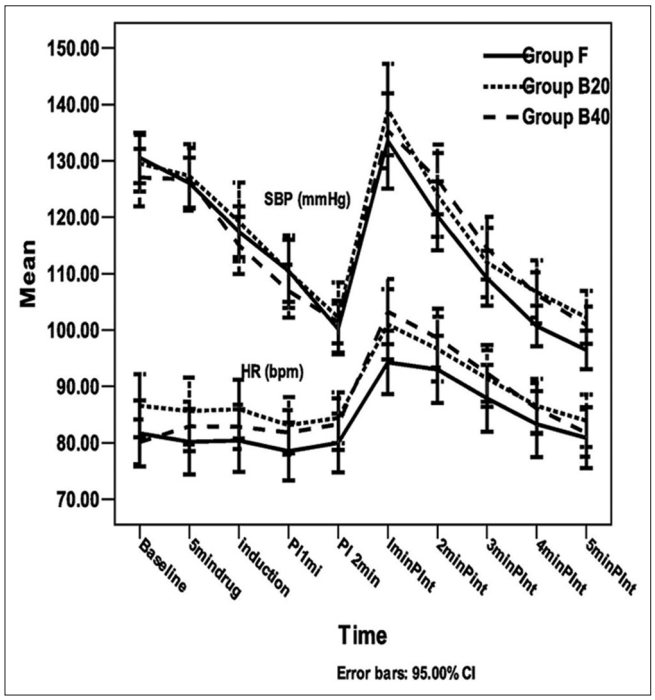

Figure 4: Changes in heart rate and systolic blood pressure. No statistically significant difference in the three groups

patients (7.5%) in Group F and one patient (2.5%) in Group B20 had mild itching. O_2 desaturation was observed in nine patients (22.5%) in Group F, six patients (15%) in Group B20 and four patients (10%) in Group B40. This was not statistically significant (P=0.28). No patient complained of intraoperative awareness.

DISCUSSION

The results of this study show that the reduction in the induction dose of propofol with 20 μg/kg of butorphanol was comparable to fentanyl 2 μg/kg. Increasing the dose of butorphanolto 40 μg/kg had no additional reduction in the propofol requirement. The loss of response to verbal commands occurred at higher entropy values in the presence of both fentanyl and butorphanol.

Lysakowski and colleagues[3] showed that analgesic concentrations of fentanyl facilitate loss of consciousness (LOC) at lower plasma effect-site concentrations. Mi and co-workers[6] also reported that fentanyl pre-treatment potentiated the effect of propofol for achieving the hypnotic end-point. They found lower propofol concentrations in the propofol + fentanyl group compared with the propofol group at responsiveness to verbal commands, loss of eyelash reflex and response to mechanical nasal membrane stimulation. The results of the present study are consistent with the results of previous studies. Pre-treatment with fentanyl 2 μg/kgreduced the induction dose of propofol to 1.1±0.50 mg/kg.

Butorphanol has been found to be a good premedicant, providing analgesia along with sedation.[10] Its lack of euphoric effects may be useful for clinical populations prone to drug-seeking behavior.[11] Because 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 cheaper than fentanyl.

Although its role as an analgesic and premedicant drug is well established in humans, there are only a few animal studies on the dose-sparing effect at induction. Two studies in dogsreported that butorphanol, along with other premedicants, significantly reduced the dose requirement of propofol at induction.[12,13] In another study in cats, premedication with butorphanol or morphine, combined with acepromazine, significantly reduced the propofol dose for induction.[14] There are no reports in humans.

Fentanyl 2 μg/kg and butorphanol 40 μg/kg have been reported to be equianalgesic.[4,15] Butorphanol 40 μg/kg produces more sedation and delays the recovery.[15] We wanted to identify the optimal dose of butorphanol that would augment the hypnotic effect of propofol without undue adverse effects such as increased sedation and delayed post-operative recovery. In our study, we administered butorphanol in two doses, i.e., 20 μg/kg and 40 μg/kg. We found that the propofol induction dose with butorphanol 20 μg/kg was 1.05±0.35 mg/kg. There was no further reduction in the induction dose of propofol by increasing the dose of butorphanolfrom 20 μg/kg to 40 μg/kg. This could have

resulted from the ceiling effect of butorphanol. A similar observation was made by Murphy and colleagues,[16] who have reported that there is a "ceiling" to the potency of nalbuphine and butorphanol as anesthetic supplements. This ceiling effect seems to be beneficial in minimizing the incidence of various side-effects like respiratory depression with antagonist–agonist opioids than with pure agonists.

Depth of sedation and alertness was assessed using the responsiveness scores of the modified OAA/S.[9] Higher sedationwas observed in both the butorphanol groups as compared with Group F. 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.[6] Butorphanol is also associated with less respiratory depression as compared with fentanyl due to its receptor profile.[17] It was observed in our study that fewer patients experienced O_2 desaturation after administration of the study drug in both butorphanol groups. MAP SpO_2 values were also higher in the two butorphanol groups than in the fentayl group, although there was no statistical difference in the three groups.

Bispectral (BIS) and SE/RE indices have been widely used to estimate the depth of anesthesia and sedation. The administration of opioids together with anesthetics may substantially change the predictive value of these EEG monitors. Sebel and colleagues[18] commented that the adjunctive use of an opioid analgesic confounds the use of BIS as a measure of anesthetic adequacy when movement response to skin incision is used as the primary endpoint. Miand co-workers[6] found higher BIS in the propofol + fentanyl group compared with the propofol group at unresponsiveness to verbal commands, loss of eyelash reflex and response to mechanical nasal membrane stimulation.

Lysakowski and colleagues also reported that LOC occurred at a higher BIS_{50} (BIS value at which 50% of the patients lost consciousness) in the presence of an opioid. One possible explanation for this may be that opioids, in the analgesic concentrations used in the study, produce minimal electrophysiological alterations on the cerebral cortex.[3] Another possible explanation as to why the entropy did not reveal the interaction between the propofol and an opioid may be that non-cortical structures that are undetectable by EEG, such as the locus coeruleus, are involved in the mechanism of the drug effect.[19]

In our study, we found that the entropy values were high when the patients had become unresponsive to verbal commands in all the three groups, a finding similar to previous studies. RE and SE at induction was higher than 60 in all the three groups.

There was a significant attenuation of hypertensive response to intubation in all the three groups. The major drawback of propofol is reduction in blood pressure with the standard induction dose of propofol. A typical induction dose of propofol (2 mg/kg) results in an approximate 30% reduction in SBP.[1,15] Reduction in the requirement of induction dose reduces the hemodynamic effects of propofol. The incidence of fall in blood pressure to <30% was lower in all the three groups. The hemodynamic stability with both doses of butorphanol was comparable to fentanyl.

The recovery profile of the patients was not included in this study due to the heterogeneity of the duration of surgical procedures. The earlier studies have shown that there was no significant difference in the recovery profile between butorphanol 20 μg/kg and fentanyl 2 μg/kg. Higher doses of butorphanol (40-60 μg/kg) resulted in prolonged sedative effects and delayed discharge.[15,20]

We conclude that butorphanol 20 μg/kg reduces the induction requirement of propofol comparable to that of fentanyl 2 μg/kg and confers hemodynamic stability at induction and intubation. It is therefore an acceptable alternative opioid to fentanyl as an adjuvant to balanced general anesthesia. Increasing the dose of butorphanolto 40 μg/kg does not provide additional advantage.

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