Original Article

Bispectral index-guided comparison of dexmedetomidine and fentanyl as an adjuvant with propofol to achieve an adequate depth for endotracheal intubation – A double-blind randomised controlled trial

Address for correspondence:
Dr. Swati Singh,
E/73-B, Srikrishnapuri,
Near Basawan Park,
Patna - 800 001, Bihar, India.
E-mail: drswatisingh21@gmail.com

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Annu Choudhary, Swati Singh, Swati Singh, Faseehullah Alam[1], Harsh Kumar
Department of Anaesthesiology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, [1]Department of Anaesthesiology, CISRO Hospital, Patna, Bihar, India

ABSTRACT

Background and Aims: Laryngoscopy and tracheal intubation require an adequate depth of anaesthesia. The study's primary objective was to compare the time needed to achieve the bispectral index (BIS)-guided adequate depth of anaesthesia for endotracheal intubation using fentanyl and dexmedetomidine. **Methods:** After institutional ethics committee clearance and written informed consent, this randomised study was conducted on 140 patients of either gender between 18 and 60 years who were scheduled for elective surgeries under general anaesthesia. Patients were randomised to intravenous dexmedetomidine 1 μg/kg (Group D) or fentanyl 2 μg/kg (Group F). The drugs were given as an intravenous infusion over 10 min before induction of anaesthesia. The primary outcome was the time required to achieve BIS 50. Normally distributed variables were compared using Student's *t*-test, and non-normally distributed variables were compared using the Mann–Whitney U test. Qualitative data were analysed using Chi-square/Fisher's exact test. A *P* value <0.05 was considered significant. **Results:** The time to achieve BIS 50 was lesser in Group F, 1546 (27) as compared to Group D, 1558 (11) s [mean difference (95% confidence interval (CI) 12[5.11, 18.89]), $P < 0.001$]. Haemodynamic parameters were comparable at all time points between both the groups, except heart rate, which was significantly lower. Propofol consumption was significantly less in group D than in group F [125.9 (25.36) versus 157.3 (42.80) mg, respectively, mean difference (95% CI) 31.4 (-44.16 to -20.63) $P < 0.001$)]. **Conclusion:** Dexmedetomidine achieves BIS 50 faster and has a propofol-sparing effect as compared to fentanyl.

Keywords: Bispectral index, depth of anaesthesia, dexmedetomidine, fentanyl, intubation, laryngoscopy, propofol, tracheal

INTRODUCTION

Laryngoscopy can be associated with haemodynamic alteration, which needs to be minimised by maintaining the proper depth of anaesthesia.[1] Adjuvants always accompany intravenous (IV) induction agents to produce synergy at a lower dose. Fentanyl is the most commonly used drug before propofol induction for balanced anaesthesia, but it is not devoid of sinister side effects like chest wall rigidity.[2,3] Hence, achieving the same outcome with other medications is desirable.

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Of late, dexmedetomidine, a selective and potent alpha-2 adrenoceptor agonist, has been extensively used for its sedative, analgesic, sympatholytic, and anxiolytic properties. The drug has demonstrated encouraging results in lowering the induction dose of propofol and the intraoperative requirement for anaesthetic agents.[4,5] To our knowledge, this is the first study comparing dexmedetomidine with fentanyl as an adjuvant to assess its role in achieving an adequate depth for intubation by comparing bispectral index (BIS) values.

The primary objective of our study was to compare the time required to achieve an adequate depth of anaesthesia,[6] that is, the BIS 50 level, using IV fentanyl and dexmedetomidine. We also compared the haemodynamic parameters (heart rate, mean arterial pressure, oxygen saturation) between both groups at various time points and the total IV propofol required to achieve BIS 50. We hypothesised that administering IV dexmedetomidine as an adjuvant with IV propofol would assist in achieving an early and adequate depth of anaesthesia for laryngoscopy and endotracheal intubation.

METHODS

This randomised, double-blind, controlled study was conducted from September 2021 to May 2022 after obtaining approval from the institutional ethics committee (vide approval number 67/IEC/IGIMS/2021 dated 23/03/2021). The study was registered with the Clinical Trials Registry-India (vide registration number CTRI/2021/07/034887, https://www.ctri.nic.in, 15/07/2021) and carried out following the principles of the Declaration of Helsinki, 2013 and good clinical practice.

The study included 140 American Society of Anesthesiologists (ASA) physical status I/II patients of both genders, aged 18 to 60 years, scheduled for elective surgeries under general anaesthesia. Exclusion criteria were patients with uncompensated cardiovascular, pulmonary, neurological, hepato-renal, endocrine disorders, and allergy to study drugs as well as any substance abuse disorders.

Randomisation to two groups was performed using a computer-generated random number table (http://www.random.org). The group allocation was written on a page, folded and concealed serially in a sealed opaque envelope. Before enrolment, the patient signed an informed and written consent (the study protocol was explained in their native language) to participate in the study and use patient data for research and educational purposes.

All patients were fasted according to ASA fasting guidelines. No sedative premedication was administered on the day of surgery. Standard ASA monitors (electrocardiogram, non-invasive arterial blood pressure, end-tidal carbon dioxide, and pulse oximetry) and BIS were attached before the induction of anaesthesia. The skin of the forehead was cleaned with an alcohol swab and dried with a gauze before applying a disposable BIS-quatro sensor strip (Covidien Medical Systems Inc., Mansfield, MA, USA) on the forehead in accordance with the manufacturer's instructions. BIS was monitored and recorded using a BIS module (Covidien BIS LoC2 channel OEM Module, Mansfield, MA, USA) every second, and all BIS activities during the study duration were studied for analysis.

The study drug was prepared in 100 ml of saline by an independent anaesthesiologist who was not involved further in the study. A peripheral IV line was established, and the study drug was infused in 100 ml saline over 10 min. Patients in Group D received IV dexmedetomidine 1 μg/kg, and patients in Group F received IV fentanyl 2 μg/kg. After 15 min, anaesthesia induction was started by another anaesthesiologist. IV propofol 2 mg/kg and cisatracurium 0.15 mg/kg were administered, and tracheal intubation was attempted with an appropriate-size endotracheal tube in 3 min, only if BIS ≤50 was achieved.[6] If BIS >50, a rescue dose of IV propofol 1 mg/kg was given at the time of tracheal intubation. After tracheal intubation, all patients were given IV fentanyl 2 μg/kg for intra-operative analgesia, and patients were put on controlled ventilation with tidal volumes of 6 ml/kg and a respiratory rate of 12 per minute. Maintenance of anaesthesia was done with oxygen and air at a ratio of 1:1 with isoflurane. At the end of the surgery, residual neuromuscular blockade was reversed, the trachea was extubated and the patient was shifted to the postanaesthesia care unit.

The primary objective was to compare the time required to achieve an adequate depth of anaesthesia,[6] that is, the BIS level of 50, using IV fentanyl and dexmedetomidine. The secondary outcomes measured included haemodynamic parameters and total propofol required in each group to achieve BIS 50.

Demographic variables, that is, age, weight, gender, ASA physical status, the time required to achieve BIS 50 (from the start of infusion of the study drug), and rescue doses of propofol necessary to achieve BIS50, were noted. Haemodynamic parameters, that is, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and peripheral arterial oxygen saturation (SpO_2), were noted at various time points (before the start of induction, after induction, just before intubation, and 1, 3, and 5 min following intubation). The patients were observed for any adverse effects throughout the procedure and post-operatively. Any event of haemodynamic variation, that is, intra-operative hypotension (blood pressure <20% of baseline), hypertension (blood pressure >20% of baseline), bradycardia (HR <60/min), or tachycardia (HR >100/min), was recorded and treated with IV mephentermine 6 mg boluses, labetalol 5 mg boluses, atropine 0.6 mg, and esmolol 10 mg, respectively.

During the literature review, we could not find any study comparing the time required to achieve BIS 50 by using IV fentanyl and dexmedetomidine as adjuvants with propofol for anaesthesia induction. We conducted a pilot study with 20 patients; 10 patients received an IV propofol and fentanyl combination, and the other 10 patients received an IV propofol and dexmedetomidine combination. The mean [standard deviation (SD)] time to achieve BIS 50 was 25.76 (0.32) min in the dexmedetomidine group and 25.9 (0.22) min in the fentanyl group. To statistically show this difference, while keeping an α error of 0.05 and the power of study at 80%, 61 patients were required in each group. Keeping a 15% attrition rate, it was decided to keep 70 patients in each group.

The Statistical Package for Social Sciences (SPSS) program was used for statistical analysis (version 22.0 NY: International Business Machines Corp, USA). Categorical variables (gender, ASA physical status) were expressed as frequency (%), and the Chi-square test was applied to test the significance of association between groups and variables. Continuous variables (time to achieve BIS 50, propofol requirements) were expressed as mean (SD) with 95% confidence intervals (CIs). A T-test was performed to compare the mean of variables between the two groups. Repeated measure analysis of variance was performed to test the HR and MAP at different observation points for group and time separately and as an interaction effect of group and time. The non-parametric tests (Wilcoxon–Mann–Whitney U-test) were used to compare independent samples (BIS value at observed time points). Missing observations were excluded from the analysis.

RESULTS

Out of 150 patients screened for the study, only 140 were enroled and completed the final analysis, as seen in the Consolidated Standards of Reporting Trials (CONSORT) diagram [Figure 1]. Both groups had comparable demographic data [Table 1].

The mean (SD) time to achieve BIS 50 was 1546 (27) s in group D, compared to 1558 (11) s in group F [mean difference (95% CI 12 (5.11, 18.89), $P = 0.001$)] [Figure 2]. The decrease in BIS value started with the IV infusion of fentanyl and dexmedetomidine before anaesthesia induction. The reduction in BIS values was significantly lower for group D compared to group F at various time points, with the largest difference found at 25 min mean (SD),

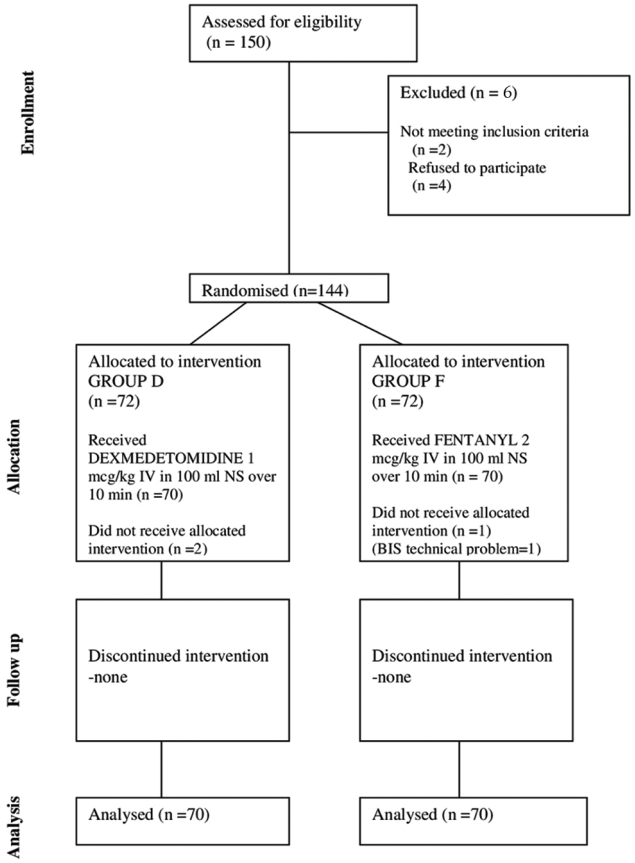

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participants. D = Dexmedetomidine, F = Fentanyl, IV = Intravenous, NS = Normal Saline, n = Number of cases, BIS = Bispectral Index

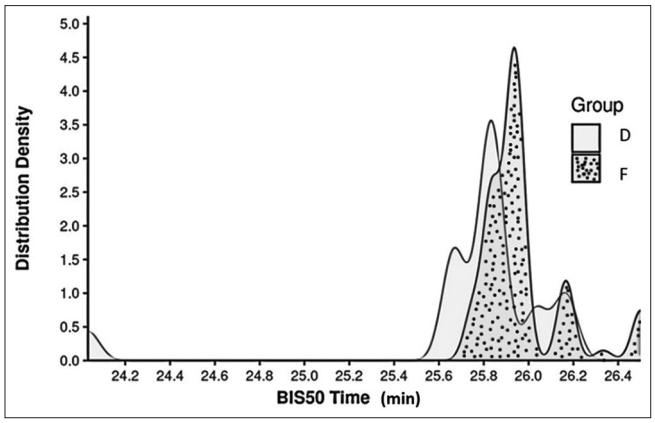

Figure 2: Density plot depicting the distribution of BIS50 Time (minutes). D, Dexmedetomidine, F, Fentanyl, BIS = Bispectral Index, BIS50 time, the time to achieve a bispectral value of 50

Table 1: Comparison of demographic data

Characteristics	Group D (*n*=70)	Group F (*n*=70)
Age (years)	34.57 (10.04)	37.74 (11.18)
Gender (Male/Female) (*n*)	28/42	26/44
Weight (kg)	60.64 (8.28)	62.91 (6.93)
ASA physical status I/II	45/25	41/29

Data expressed as mean (standard deviation) or numbers. ASA=American Society of Anesthesiologists, *n*=Number of patients, D=Dexmedetomidine, F=Fentanyl, *n*=Number of cases

78.11 (6.6) versus 92.87 (4.93) (mean difference [95% CI] 14.76[12.81, 16.70]) ($P = 0.001$) [Figure 3].

Mean baseline haemodynamic parameters (HR, SBP, DBP, MAP, and SpO_2) were comparable in both groups. At all observed time points, no significant difference was observed between the SBP, DBP, MAP, and SpO_2 groups. The two groups differed significantly in HR at all time points ($P < 0.001$).

The mean (SD) total propofol requirement in group D was 125.9 (25.36) mg, whereas in group F, it was 157.3 (42.80) mg (mean difference [95% CI] 31.4 [-44.16, -20.63], $P < 0.001$). The number of patients requiring a rescue dose of propofol was 8 in group D compared to 37 in group F ($P = 0.001$).

No electrocardiographic changes (arrhythmias), desaturation, or hypotension were observed during the study. Bradycardia was seen in one patient in group D ($\chi 2 = 1.007$, $P = 1.000$).

DISCUSSION

In the present study, the adequate depth of anaesthesia needed for laryngoscopy and endotracheal intubation, assessed by the BIS 50 value, was achieved faster when dexmedetomidine was administered as a pre-medication with propofol as compared to fentanyl. More patients required a rescue dose of propofol in the fentanyl group as compared to the dexmedetomidine group, and the total propofol requirement was also significantly higher in the fentanyl group.

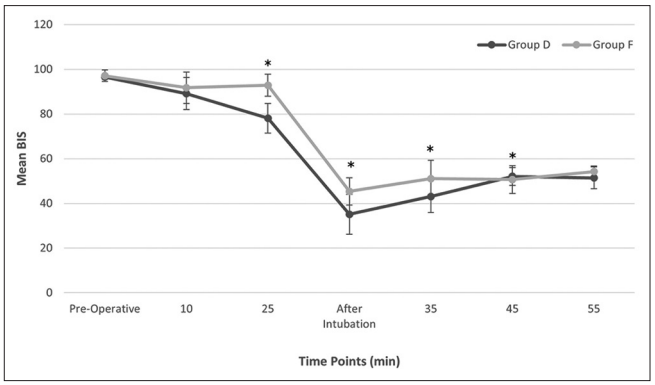

Figure 3: Comparison of BIS value changes between groups over time. D = Dexmedetomidine, F = Fentanyl, BIS = Bispectral Index. **P* value <0.001

Multiple hypotheses exist on the mechanism responsible for reducing BIS values by adding dexmedetomidine to propofol.[5,7] Yang *et al*.[7] postulated a synergistic effect of dexmedetomidine and propofol by action on the noradrenergic signal at the thalamocortical area, potentiating the activity of gamma-aminobutyric acid (GABA) α-receptors and inhibiting N-methyl-D-aspartate (NMDA)-mediated excitatory neurotransmission, respectively, for achieving the required level of unconsciousness. Our findings support the positive association between dexmedetomidine and propofol, as demonstrated by the decreased propofol requirement in the dexmedetomidine group. When dexmedetomidine was used as an adjuvant with propofol, the target BIS was achieved earlier with a smaller amount of propofol. The decreased propofol requirement can benefit patients with volume deficits and cardiac co-morbidities.

The faster achievement of BIS with the propofol-sparing effect in the dexmedetomidine group is in concurrence with the results observed by Walia *et al*.[8] They found that the total propofol requirement to achieve BIS 40-50, MAP, HR, and BIS values was significantly lower in the dexmedetomidine group than in the magnesium sulfate group.

Gu *et al*.[7] found that a lower dose of propofol was required to achieve a loss of consciousness (LOC)

when dexmedetomidine was added to propofol than when propofol was administered alone. In their study, in all three groups at LOC, BIS values [68 (4.1) in the 1 μg group, 67.5 (3.5) in the 0.5 μg group, and 60.5 (3.8) in the placebo group] were not sufficient for the depth required for painful intervention such as laryngoscopy. LOC represents a wide range on the spectrum of depth of sedation, from mild sedation to a deep hypnotic state. Achieving LOC (eliciting loss of verbal response) would not be enough to ensure the adequate depth of anaesthesia required to blunt the sympathetic response. The possible explanation for this is that the addition of adjuvants like opioids and dexmedetomidine to propofol before induction leads to early LOC before an adequate depth of anaesthesia is achieved.[7,9] Therefore, we believe a quantitative and easily reproducible method is required to yield higher-quality monitoring. Thus, the superiority of our methodology over other similar studies lies in the choice of BIS 50 as a primary endpoint in our research since it is reliable and can be continuously monitored. The use of BIS 50 as a target to attempt laryngoscopy has not been explored widely in randomised trials despite the large body of work that has been undertaken on the depth of anaesthesia and dexmedetomidine.

The combined effect of opioids and propofol on BIS is unclear. Factors like low cost, high potency, and excellent analgesic effect make fentanyl a favourable choice as part of balanced anaesthesia.[9,10] Fentanyl is considered a comprehensive pre-medication, but we found it to be insufficient for providing an adequate depth of anaesthesia at a dose of 2 μg/kg. It needed to be supplemented during the painful intervention. Patients in the fentanyl group required additional doses of propofol and took a longer time to reach BIS 50 values. This increased propofol requirement can lead to more complications in the patient population. Jain *et al*.[11] have advocated using BIS monitoring as an essential parameter during laryngoscopy and intubation. Rajasekhar *et al*.,[12] in their study, compared the haemodynamic responses to laryngoscopy and intubation using different laryngoscopy blades and stated that the depth of anaesthesia is more important than newer devices to prevent haemodynamic responses during laryngoscopy and intubation.

The major limitation of our study was that we did not use target-controlled infusion of the study drugs; therefore, we could not correlate drug plasma concentration with BIS values. Another limitation was that further comparison of the effects of both drugs as adjuvants on the peri-operative analgesic requirements in both groups was not observed.

CONCLUSION

Our study demonstrates that dexmedetomidine, when compared with fentanyl as an adjuvant with propofol, achieves BIS 50 in less time and with a total dose of propofol.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

ORCID

Annu Choudhary: https://orcid.org/0000-0003-2893-2267
Swati Singh: https://orcid.org/0000-0003-2482-7902
Swati Singh: https://orcid.org/0000-0002-8382-5977
Faseehullah Alam: https://orcid.org/0000-0002-4859-5459
Harsh Kumar: https://orcid.org/0000-0005-6497-2209

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