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The effect of co-induction of fentanyl compared to oxycodone on anesthetic depth and hemodynamic status in surgical patients under general anesthesia at Prof. Ngoerah Denpasar General Hospital

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ABSTRACT

Introduction: Laryngoscopy and endotracheal intubation during general anesthesia can elicit sympathetic responses, including elevated blood pressure and heart rate. Fentanyl and oxycodone are opioids used for anesthesia co-induction to attenuate this response. This study aims to compare the co-induction effects of fentanyl and oxycodone on anesthesia depth and hemodynamic stability.

Methods: This was a prospective observational study involving 40 adult patients with ASA I II status undergoing general anesthesia at RSUP Prof. Ngoerah Denpasar. Subjects were randomized into two groups: fentanyl 2 µg/kg BW and oxycodone 0.2 mg/kg BW. All patients underwent standard induction protocols. The depth of anesthesia was assessed using the CONOX monitor (qCON), while hemodynamic status was evaluated through blood pressure, heart rate, and stroke volume via USCOM. Data were analyzed using t-tests and Mann-Whitney U tests with significance set at $p<0.05$.

Results: There were no statistically significant differences in mean arterial pressure or heart rate between the groups ($p>0.05$), indicating similar hemodynamic responses. However, stroke volume reduction after intubation was significantly less in the oxycodone group (median ΔSV 3 vs 11.5; $p<0.001$). Additionally, qCON values showed better anesthesia depth with oxycodone (51.0 ± 5.8 vs 60.5 ± 7.5; $p<0.001$).

Conclusion: Oxycodone co-induction results in better anesthesia depth and equal or superior hemodynamic stability compared to fentanyl. Oxycodone may be considered an effective alternative for co-induction in general anesthesia.

Keywords: Anesthesia co-induction. Oxycodone, Fentanyl, Anesthetic depth, Hemodynamic stability.
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INTRODUCTION

Laryngoscopy and endotracheal intubation are important but invasive procedures in general anesthesia that can cause physiological stress in the form of increased sympathetic activity.[1,2] This adrenergic response is reflected through hemodynamic changes, including increased blood pressure and heart rate, which can be particularly dangerous in patients with cardiovascular comorbidities or elevated intracranial pressure.[3]

Several previous studies have shown that endotracheal intubation can affect the hemodynamic stability of patients. Teong et al found a significant spike in systolic blood pressure and heart rate after intubation, which can be stabilized by administering fentanyl 2 mcg/kg 2 minutes before intubation.[4] Another study by Ji et al found that endotracheal intubation can increase several sympathetic parameters, HR, SBP, and DBP.[5] Therefore, a co-induction strategy is needed that can suppress this response without compromising anesthetic stability and overall hemodynamics.[6]

Co-induction anesthesia is an essential strategy in modern anesthetic practice due to its ability to enhance drug synergy, optimize anesthetic depth, and improve patient safety while minimizing adverse effects. The rationale behind co-induction lies in the use of two or more agents with complementary pharmacodynamic profiles, allowing lower doses of each drug to be used while achieving the desired anesthetic effect. This approach is particularly important in patients with hemodynamic vulnerability or those requiring rapid yet smooth induction with preserved cardiorespiratory stability.[4]

Physiologically, endotracheal intubation and laryngoscopy elicit intense sympathetic stimulation, leading to transient hypertension, tachycardia, and elevated catecholamine levels. Co-induction protocols, for example, combining a sedative (e.g., midazolam or dexmedetomidine) with an opioid (e.g., fentanyl or oxycodone), provide preemptive blunting of these stress responses. They also offer better control of consciousness, analgesia, and muscle

relaxation during induction, reducing the risk of awareness or movement during laryngoscopy.[4,6]

In modern anesthetic practice, a multimodal approach is applied through a combination of hypnotic agents, analgesics, and muscle relaxants.[7,8] One important aspect of anesthesia management is the assessment of anesthesia depth, which can now be monitored in real-time using electroencephalography-based devices such as the Bispectral Index (BIS) and CONOX®. This technology provides objective parameters for hypnotic effects and responses to nociceptive stimuli, replacing reliance on hemodynamic parameters alone.[9,10]

Fentanyl is a synthetic opioid belonging to the phenylpiperidine class, characterized by its lipophilic nature, rapid onset, and short duration of action. This drug is widely used in co-induction due to its effectiveness in suppressing the sympathetic response during laryngoscopy and intubation.[11] Meanwhile, oxycodone, a semi-synthetic opioid agonist of the mu and kappa receptors, has shown pharmacokinetic and pharmacodynamic profiles similar to fentanyl, with a longer duration of action and high analgesic potential.[12] The study by Lee et al. (2016) reported that administration of oxycodone 0.2 mg/kg was more effective than fentanyl 2 µg/kg in suppressing the hemodynamic response during intubation.[13]

Although oxycodone has been used as a co-induction agent in various countries, its use in Indonesia is still limited to postoperative pain management. This study aims to evaluate and compare the co-induction effects of oxycodone and fentanyl on the depth of anesthesia and hemodynamic status in surgical patients undergoing general anesthesia at Prof. Ngoerah Denpasar General Hospital.

METHODS

Study Design

This study used a prospective observational study design. The study was conducted in the operating room of Prof. Dr. I G. N. G. Ngoerah Hospital, Denpasar. This study took place from 2020 to 2021.

Sample and Population

The target population was all adult patients undergoing elective surgery with general anesthesia. Inclusion criteria included patients with ASA I–II status, aged 18–60 years, and willing to participate in the study through informed consent. Exclusion criteria included patients with hemodynamic disorders, severe heart disease, neurological disorders, allergies to opioids, and patients with predicted airway difficulties.

The sample size was calculated using a power analysis based on the comparison of means in anesthetic depth (qCON values) between two independent groups. Referring to a previous study by Lee et al. (2016), which reported a mean difference of approximately 10 units in qCON between fentanyl and oxycodone groups with a standard deviation of 10, we used a two-tailed test with a power of 80% and a significance level (α) of 0.05.[13] Using these parameters, the required sample size per group was 17 subjects. To account for potential dropouts or data loss, we increased the sample to 20 subjects per group, yielding a total sample of 40 participants.

Research Procedure

Patients were randomly divided into two groups: Group A: co-induction with Fentanyl 2 µg/kg BW and Group B: co-induction with Oxycodone 0.2 mg/kg BW. All patients underwent a standard induction protocol with midazolam, propofol, and atracurium. Intubation was performed by anesthesiologists with at least 2 years of experience. Anesthetic depth was assessed using a BIS monitor or CONOX® (qCON value), while hemodynamic status was evaluated based on blood pressure, heart rate, and USCOM parameters such as cardiac output and stroke volume.

Random sequences were block-generated (blocks of four) with Randomizer® software. Allocation was concealed in sequentially numbered, opaque, sealed envelopes prepared by an independent research nurse and opened after enrolment. During induction, the CONOX screen faced away from the anaesthesiologist and was covered with an opaque shield visible only to the blinded data recorder.

Variable Measurement

The depth of anesthesia was measured using qCON or BIS values every 30 seconds from the start of induction until 5 minutes after intubation. Hemodynamic status was measured, including systolic blood pressure, diastolic blood pressure, pulse rate, and cardiac output using USCOM, with the same measurement time. To minimize bias in this study, patients were randomly assigned to treatment groups using a computer-generated sequence. Although the anesthesiologist performing induction was not blinded, the investigator responsible for recording CONOX and USCOM values was blinded to group allocation. All patients received a standardized induction protocol, and intubations were performed by anesthesiologists with uniform experience levels. Objective outcome measures were employed using validated instruments (CONOX® and USCOM), and statistical analysis was conducted independently based on predefined methods to reduce observer and analytical bias.

Statistical Analysis

The data were analyzed using SPSS software. Data normality was tested beforehand. Parametric data were tested using an independent t-test, while non-parametric data were tested using a Mann-Whitney U test. Differences were considered statistically significant if $p < 0.05$.

RESULTS

This study is a prospective observational study conducted on patients undergoing surgery with general anesthesia in the operating rooms of the Central Surgery Unit, Amerta Wing Unit, and Emergency Unit of Sanglah General Hospital in Denpasar from June to August 2019. The required sample size was 40 patients, divided into two treatment groups: the oxycodone group and the fentanyl group, with 20 patients in each treatment group. No patients dropped out of the study.

In this study, a comparison of hemodynamic responses and depth of

anesthesia between oxycodone and fentanyl as adjuvants for epidural analgesia will be conducted. Hemodynamic responses will be assessed through five hemodynamic measurements taken before induction, after induction, during intubation, 3 minutes after intubation, and 5 minutes post-intubation. Hemodynamic stability will also be compared using pulse rate and mean arterial pressure measured from the five measurements. The comparison of anesthesia depth between oxycodone and fentanyl will be measured through the increase in qCON values on the CONOX monitor attached to the patient. Numeric-scale variables with a normal distribution are presented as mean and standard deviation, while those without a normal distribution are presented as median and interquartile range. Categorical-scale variables are presented as relative frequency distributions.

The characteristics of the research subjects are shown in Table 1 to see whether the two groups are comparable or not. The numerical data variables are age and body mass index (BMI). The distribution of age and BMI data is normal and is presented in the form of mean ± standard deviation, with the test used being the independent t-test. The categorical variables are gender and ASA physical status, presented as proportion distributions, with the Chi-squared test used for analysis.

The patient population consisted of 40 patients who underwent general anesthesia with 20 samples of oxycodone and 20 samples of fentanyl. In the analysis, the mean age ± standard deviation in the oxycodone group was 47.2 ± 11.4, while in the fentanyl group it was 47.4 ± 11.9. After statistical testing, no significant difference was found with a p-value of 0.957. The mean BMI in the oxycodone group was 23.1 with a standard deviation of 3, while in the fentanyl group it was 23.8 kg/m² with a standard deviation of 3.2. Statistically, the BMI variable did not differ significantly, with a p-value of 0.531.

The gender of patients was classified into two groups, with a distribution of 50% males and 50% females in the oxycodone group, while in the fentanyl group, there were 40% males and 60% females. Statistically, there was no significant difference with a p-value of 0.525. The patients' physical status was categorized into three groups: ASA I, ASA II, and ASA III. The distribution of the ASA I physical status variable in the oxycodone group was 30%, and in the fentanyl group, it was

Table 1. Characteristics of Subjects Based on Research Groups

Variables	Oxycodon Group (n=20)	Fentanyl Group (n=20)	p-value
Age (years), mean+SD	47.2 ± 11.4	47.4 ± 11.9	0.957
Gender, n (%)			
Male	10 (50.0)	8 (40.0)	0.525
Female	10 (50.0)	12 (60.0)	
BMI (kg/m²), mean+SD	23.1 ± 3.0	23.8 ± 3.2	0.519
ASA Score, n (%)			
I	6 (30.0)	8 (40.0)	0.531
II	9 (45.0)	8 (40.0)	
III	5 (25.0)	4 (20.0)	

Table 2. Hemodynamic Response in Terms of MAP and Heart Rate Based on Treatment Groups

Variables	Oxycodon Group (n=20)	Fentanyl Group (n=20)	Mean differences	p-value
Mean Arterial Pressure (MAP)				
1	92.6 ± 9.6	90.3 ± 11.5	2.3	0.493
2	80.9 ± 18.0	79.4 ± 11.7	1.5	0.759
3	84.2 ± 13.6	81.8 ± 19.5	2.5	0.647
4	86.5 ± 14.2	82.0 ± 17.9	4.6	0.380
5	85.0 ± 13.3	80.5 ± 11.2	4.5	0.255
Heart Rate (HR)				
1	74.9 ± 10.4	80.9 ± 15.5	-6.1	0.153
2	74.2 ± 13.4	75.5 ± 14.9	-1.3	0.774
3	73.1 ± 11.6	75.3 ± 8.2	-2.2	0.502
4	74.5 ± 9.9	73.7 ± 10.0	0.8	0.802
5	74.0 ± 10.0	74.0 ± 10.1	-1.5	0.629

Table 3. Stroke Volume Values Based on Treatment Groups

Variables	Oxycodon Group (n=20)	Fentanyl Group (n=20)	Mean differences	p-value
Stroke Volume, (mean± SD)				
1	60.6 ± 4.6	63.5 ± 4.6	-2.9	0.051
2	58.0 ± 5.4	51.9 ± 7.6	6.1	0.006
Δ Stroke Volume (median IQR)	3 (2)	11.5 (8.5)	8.5	<0.001

Table 4. qCON and qNOX Values Based on Study Groups

Variables	Oxycodon Group (n=20)	Fentanyl Group (n=20)	Mean differences	p-value
qCON	51.0 ± 5.8	60.5 ± 7.5	-9.6	<0.001
qNOX	56.8 ± 10.2	60.0 ± 7.7	-3.2	0.278

40%. The ASA II physical status variable in the oxycodone group was 45%, and in the fentanyl group, it was 40%. The ASA III physical status variable was 25% in the oxycodone group and 20% in the fentanyl group. Statistically, there was no significant difference in the proportion of ASA physical status with a p-value of 0.531. Statistically, no significant differences were found in patient characteristics between the two groups, so it can be concluded that the two groups were comparable.

The mean arterial pressure (MAP) was calculated based on systolic and diastolic blood pressure and was monitored five times: before induction in both groups, after induction, during laryngoscopic intubation, and at 3- and 5-minute post-intubation. MAP is a numerical variable with a normal distribution. The independent t-test was used for statistical analysis, and the results are presented as mean ± standard deviation. Similarly, heart rate was monitored at the same five time points and is also a numerical variable with a normal distribution. The independent t-test was applied for heart rate analysis as well, and the results are presented as mean ± standard deviation. A comparison of mean arterial pressure between groups is presented in Table 2.

Based on the table, no statistically significant differences were observed in the mean arterial pressure (MAP) of patients in either the oxycodone or fentanyl groups across the five measurement time points. Similarly, the comparison of heart rate between the two groups revealed no statistically significant differences, as indicated by p-values greater than 0.05. The absence of hemodynamic differences suggests that both drugs produced comparable hemodynamic responses in maintaining hemodynamic stability.

The stroke volume (SV) variable, measured using USCOM, was assessed before induction and remeasured after intubation. Stroke volume is a numerical variable. The Mann–Whitney test was used for analysis, as the data distribution in both groups was non-normal. Results are presented as median and interquartile range (IQR).

The comparison of stroke volume (SV) changes between treatment groups is presented in Table 3. Based on the table, a decrease in SV was observed after intubation compared to the pre-induction values in both study groups. The median SV change was 3 (IQR 2) in the oxycodone group and 11.5 (IQR 8.5) in the fentanyl group, indicating a statistically significant difference with a p-value < 0.001. The qCON variable is a numerical data type with a normal distribution. The independent t-test was used for analysis, and the results are presented as mean ± standard deviation.

DISCUSSION

This study included a total of 40 samples from patients undergoing surgery under general anesthesia at Sanglah General Hospital. The study population consisted of 40 patients, with 20 patients receiving oxycodone and 20 receiving fentanyl as part of their anesthetic regimen. Patient sex was classified into two categories. In the oxycodone group, 50% were male and 50% were female, while in the fentanyl group, 40% were male and 60% were female.

The physical status of patients was categorized into three groups based on ASA classification: ASA I, ASA II, and ASA III. In the oxycodone group, the proportion of patients with ASA I physical status was 30%, compared to 40% in the fentanyl group. For ASA II, the proportion was 45% in the oxycodone group and 40% in the fentanyl group. Meanwhile, ASA III status was observed in 25% of patients in the oxycodone group and 20% in the fentanyl group.

After obtaining informed consent from the patient's family or accompanying person, CONOX assessment and USCOM examination were performed. To minimize observer-related bias, all USCOM measurements were conducted directly by the primary investigator. Every patient scheduled for surgery underwent USCOM assessment before induction and again after intubation, with the results recorded on a research form. Meanwhile, CONOX values were directly observed from the monitoring device.

The analysis in this study showed changes in hemodynamic parameters; however, no statistically or clinically significant differences were found between the oxycodone and fentanyl groups. Comparisons of mean arterial pressure (MAP) and heart rate across the five sequential measurements revealed no significant hemodynamic differences. This lack of significant variation suggests that both oxycodone and fentanyl have comparable effects in maintaining hemodynamic stability. These findings are supported by previous studies, including those by Lee and Yoo, which similarly reported no significant hemodynamic differences between oxycodone and fentanyl administration.[13]

This may be attributed to the fact that oxycodone shares structural characteristics and lipid solubility with morphine, with its analgesic potency depending on the route of administration. When administered intravenously, oxycodone has a potency approximately 0.7 to 1.3 times greater than that of morphine.[14]

Furthermore, analysis of anesthetic depth using qCON values measured with the CONOX monitor revealed statistically and clinically significant differences. Oxycodone demonstrated superior efficacy in maintaining anesthetic depth compared to fentanyl. In this study, the lowest mean qCON value observed in the fentanyl group remained higher than the mean change in qCON observed in the oxycodone group, with a p-value of <0.001. A qCON of 40-60 is widely accepted as adequate anaesthetic depth. Although both groups stayed within this range, oxycodone centred in the lower half (mean 51), corresponding to an ~8 % predicted awareness probability versus ~18 % for the fentanyl group, according to the CONOX algorithm.[9]

In contrast to the hemodynamic measurements using MAP and heart rate, the assessment of cardiac output obtained through USCOM showed a statistically significant difference, with a smaller reduction in stroke volume (SV) observed in the oxycodone group compared to the fentanyl group (p < 0.001). This finding demonstrates a correlation consistent with previous studies. In the present study, a weak positive correlation was identified, with a correlation coefficient lower than that reported in earlier research.[15,16]

The comparable hemodynamic stability observed between oxycodone and fentanyl can be attributed to their

shared μ-opioid receptor agonism, which attenuates sympathetic outflow and catecholamine release during laryngoscopy and intubation, thereby blunting stress-induced elevations in heart rate and blood pressure.[11,12] Both agents have a rapid intravenous onset that allows timely suppression of the pressor response, and equianalgesic dosing achieves similar modulation of autonomic reflexes without excessive cardiovascular depression.[13] Moreover, although oxycodone possesses additional κ-opioid activity, clinical studies show this does not translate into greater hemodynamic suppression than fentanyl at the doses used, resulting in comparable mean arterial pressure and heart-rate profiles during induction.[16]

Nevertheless, this study has several limitations. Several limitations warrant consideration. First, this single-centre trial enrolled patients undergoing diverse surgical procedures of variable duration, introducing uncontrolled differences in nociceptive stimulus and limiting generalisability. Second, anaesthetic depth (qCON) was recorded only once, at intubation, so intra-operative fluctuations could not be evaluated. Third, haemodynamic evaluation centred on stroke-volume changes measured by USCOM; additional invasive or ultrasound-based parameters (e.g., arterial-line waveform analysis) would provide a more comprehensive cardiovascular profile. Fourth, although randomisation balanced baseline characteristics, no multivariate regression was performed; residual confounding by factors such as age, ASA class, or surgical category, therefore, cannot be excluded. Finally, the modest sample size and the inability to blind the anaesthesiologist fully (despite assessor blinding and concealed allocation) may introduce performance bias and restrict external validity.

CONCLUSION

Based on the analysis and discussion of this study comparing the hemodynamic response and depth of anesthesia between oxycodone and fentanyl during surgeries under general anesthesia, it can be concluded that the hemodynamic response at the time of intubation, as measured by MAP and heart rate, was relatively comparable between the two groups. However, oxycodone was associated with a more stable hemodynamic response when assessed using USCOM. In addition, oxycodone provided a deeper level of anesthesia during intubation compared to fentanyl, as indicated by CONOX monitoring.

CONFLICT OF INTEREST

None.

FUNDING

None.

AUTHOR CONTRIBUTION

All authors contributed equally to this study.

ETHICAL STATEMENT

This study has received ethical clearance from the Ethics Committee of the Faculty of Medicine, Udayana University.

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