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COMPARISON OF THREE DIFFERENT DOSES OF REMIFENTANIL TO SUPPRESS PRESSOR RESPONSE DURING LARYNGOSCOPY AND INTUBATION

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ABSTRACT

Objective: Laryngoscopy and endotracheal intubation violate the patient's protective airway reflexes and induce a transient but marked sympathetic pressor response characterized by tachycardia and hypertension. The aim of this randomized prospective study was to evaluate and identify the optimal bolus dose among three different doses of remifentanil (0.5 μg/kg, 1 μg/kg, and 2 μg/kg) to suppress this acute cardiovascular stress response during general anaesthesia induction.

Patients And Methods: A cohort of 90 patients of ASA physical status I and II, aged 18 to 65 years, scheduled for elective general surgical procedures under general anaesthesia, were enrolled and randomly assigned to three parallel groups of 30 patients each: Group R1 received remifentanil 0.5 μg/kg, Group R2 received 1 μg/kg, and Group R3 received 2 μg/kg. Anaesthesia was induced with intravenous propofol 2mg/kg, and muscle relaxation was achieved with succinyl choline 1 mg/kg. Hemodynamic variables, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), were closely tracked from baseline up to 60 minutes post-intubation. Side effects and complications were documented.

Results: Following laryngoscopy and tracheal intubation, a highly significant increase in heart rate and arterial pressures occurred in Group R1 (0.5 μg/kg), confirming inadequate protection against the sympathetic surge at this dose level. Groups R2 (1 μg/kg) and R3 (2 μg/kg) both demonstrated excellent suppression of the pressor response. However, Group R3 was associated with a significantly higher incidence of intraoperative hypotension (23.33%) and clinically significant bradycardia(13.33%) compared to Groups R1 and R2 ($p < 0.05$). Perioperative complications remained minimal and statistically comparable across all groups.

Conclusions: Remifentanil administered as a bolus dose of 1 μg/kg provides the most favorable clinical balance, offering optimal and highly effective attenuation of the airway-circulatory pressor reflex while maintaining hemodynamic stability without inducing excessive cardiovascular depression or bradycardia.

KEYWORDS: Laryngoscopy, Endotracheal intubation, Pressor response, Remifentanil, Hemodynamic stability

INTRODUCTION

Securing an unobstructed airway via direct laryngoscopy and endotracheal intubation (EI) is considered the gold standard for management during elective and emergency surgeries under general anaesthesia, as well as within the intensive care unit. However, these vital procedures violate the patient's highly sensitive protective airway reflexes by pressing on the base of the tongue, lifting the epiglottis, and stimulating the tracheobronchial tree.1 This mechanical distortion triggers a marked central sympathetic reflex pathway.2

Afferent signals from pharyngeal and laryngeal structures are transmitted via the glossopharyngeal (IX) and vagus (X) nerves directly to the vasomotor center. This results in an immediate increase in efferent sympathetic discharge and a massive release of endogenous catecholamines—primarily norepinephrine and epinephrine—from sympathetic nerve endings and the adrenal medulla.3-5 This acute sympathoadrenal response manifests as a sudden spike in blood pressure, heart rate, and myocardial contractility, commonly referred to as the pressor response. Typically, this reflex initiates at around 15 seconds, peaks at 45 seconds, and subsides naturally within 5 minutes. While clinically benign in healthy patients, this transient hyperdynamic response can cause substantial morbidity in individuals with pre-existing systemic hypertension, coronary artery disease, or intracranial pathologies by critically increasing myocardial oxygen consumption and escalating risks for left ventricular failure, myocardial infarction, arrhythmias, or cerebral haemorrhage.6

Consequently, identifying a safe, prompt, and predictable pharmacological countermeasure is essential. Modern anaesthetic protocols rely on adjunct opioids to blunt this central mechanism. Remifentanil is a selective, ultra-short-acting μ-opioid receptor agonist with a rapid onset (peak effect in 1–1.6 minutes) and a very short context-sensitive half-life (3–4 minutes), driven by non-specific plasma and tissue esterase hydrolysis.7,8 These properties make it ideal for managing intense, brief noxious stimuli like tracheal intubation. However, the optimal bolus dose required to suppress

this stress response safely in the Indian clinical landscape remains a subject of ongoing debate. This study evaluated the comparative efficacy and safety profiles of three distinct bolus doses of remifentanil within a standardized anaesthetic induction model.

Aims and objectives

Primary aims:

- To compare the following parameters among the three study groups:
- Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Electrocardiographic (ECG) changes, Peripheral Oxygen Saturation (SpO_2)
- Secondary Aims
- To assess the following adverse effects and perioperative complications: Chest wall rigidity, Bronchospasm, Shivering, Nausea and vomiting, Urinary retention, Coughing, Pruritus, Respiratory depression ,Any other drug-related adverse events.

MATERIAL AND METHODS

This prospective, randomized, double-blind clinical trial was conducted at tertiary care institute, India. Following institutional ethics and thesis committee clearance (40881/D-26/2023 Batch), written informed consent was acquired from 90 elective general surgical patients in their vernacular language. Enrolled participants met the following inclusion criteria: age between 18 and 65 years, American Society of Anaesthesiologists (ASA) physical status grade I or II, and undergoing elective procedures requiring standard general anaesthesia.

Patients were excluded if they presented with key comorbidities: uncontrolled hypertension, morbid obesity, severe hepatic or renal dysfunction, severe cardiac or endocrine disorders, or had a known history of hypersensitivity to opioids, or an anticipated or confirmed difficult airway profile. Using a computer-generated randomization schedule implemented via the sealed envelope technique, patients were distributed equally into three study group allocations (n = 30 per group):

Group R1: Received an intravenous bolus dose of remifentanil 0.5 μg/kg.

Group R2: Received an intravenous bolus dose of remifentanil 1.0 μg/kg

Group R3: Received an intravenous bolus dose of remifentanil 2.0 μg/kg.

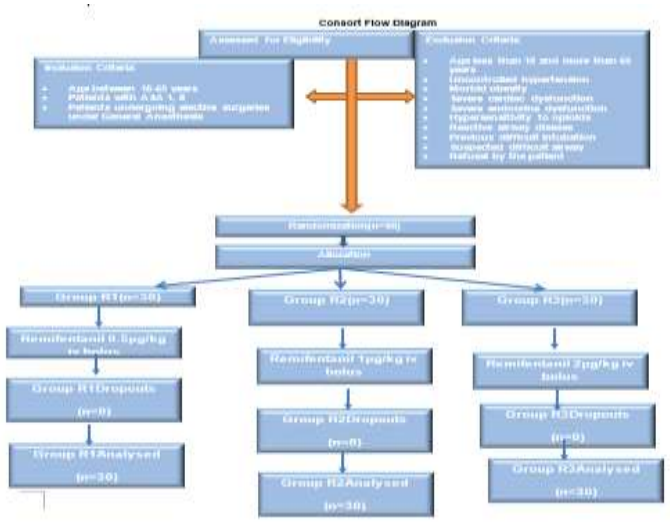
All patients fasted for a minimum of 6 hours preoperatively. Upon entering the operating room, standard monitoring metrics including non-invasive blood pressure (NIBP), pulse oximetry (SpO2), and electrocardiography (ECG) were established. Pre-induction base values were tracked. A 20-gauge intravenous line was secured, and an infusion of Ringer's lactate solution was initiated at a rate of 10 mL/kg/hr. Premedication consisting of intravenous midazolam 0.1mg/kg and glycopyrrolate 0.01 mg/kg was systematically administered to counteract potential bradycardia and provide uniform anxiolytic.

The study medication was formulated by an independent anaesthesiologist who was completely blinded to the subsequent tracking protocols. Commercial remifentanil (1 mg lyophilized powder) was reconstituted using 0.9% normal saline in a 20 mL syringe to yield a uniform concentration of 50 μg/mL, which was further precisely calibrated. Following a 3-minute period of preoxygenation with 100% oxygen, the specified group bolus dose was given slowly over 30 to 60 seconds to mitigate potential side effects, such as coughing or thoracic chest wall rigidity. Anaesthesia induction was accomplished via propofol 2 mg/kg intravenously. Neuromuscular blockade was facilitated using succinylcholine 1mg/kg. Direct laryngoscopy was performed exactly 1 minute later by a blinded investigator using standard Macintosh blades, and endotracheal intubation was completed. Anaesthesia maintenance was sustained with oxygen, nitrous oxide, and isoflurane, supplemented with vecuronium. Neuromuscular blockade was reversed at the end of surgery with neostigmine and glycopyrrolate prior to extubation.

Target vital variables (HR, SBP, DBP, MAP) were logged at baseline, pre-intubation, 1, 2, 3, 4, 5, 6, 8, 10, 15, 20, 25, 30, and 60 minutes post-intubation. Clinically significant hypotension (defined as SBP < 85 mmHg) was treated with 5 mg iv ephedrine boluses, and bradycardia (HR < 50 bpm) was managed with atropine injections. Adverse effects, such as chest wall rigidity, coughing, shivering, bronchospasm, and nausea/vomiting, were monitored continuously

Statistical Analysis

Data profiles were organized in Microsoft Excel and processed via IBM SPSS version 23.0. Continuous numeric variables are stated as Mean ± Standard Deviation (SD), and nominal categorical fields are reported as count frequencies and percentage representations. Continuous demographic fields and hemodynamic metrics were checked using one-way Analysis of Variance (ANOVA), followed by Tukey's post-hoc tests for pairwise group comparisons. Proportional distributions of categorical variables were evaluated using the Chi-square ($\chi 2$) test or Fisher's exact test. Statistical significance thresholds were set at $p < 0.05$.



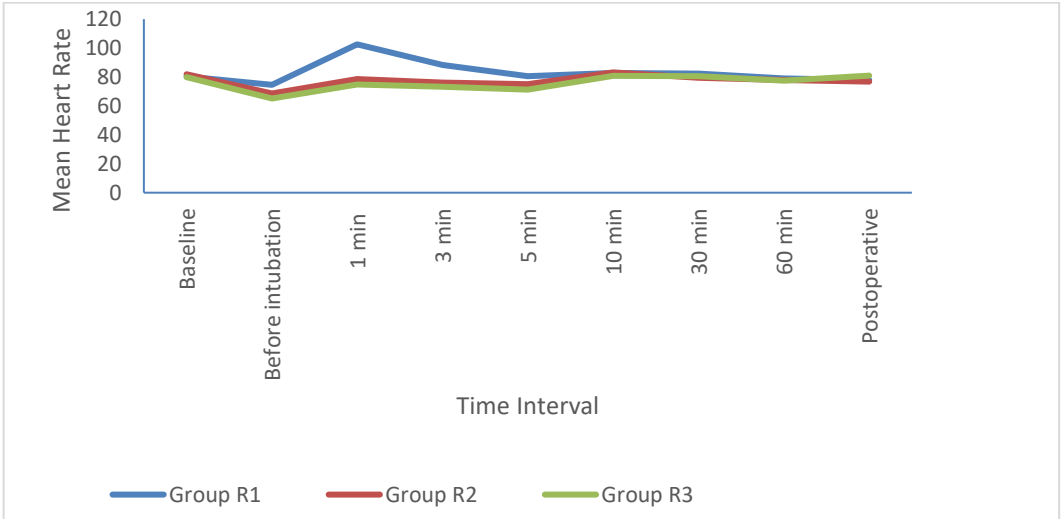
RESULTS

The groups were comparable with respect to age ($p = 0.984$), gender distribution ($\chi^2 = 1.434$, $p = 0.488$), ASA physical status ($\chi^2 = 1.067$, $p = 0.587$), body weight ($p = 0.854$), duration of surgery ($p > 0.05$), and type of surgery performed ($p = 0.998$). The mean remifentanil dose administered was 36.60 ± 6.66 µg in Group R1, 75.10 ± 13.11 µg in Group R2, and 149.07 ± 27.68 µg in Group R3, with highly significant differences among the groups ($p = 0.001$), reflecting the predefined dosing protocol. Overall, the study groups were well matched with respect to baseline demographic and clinical characteristics.

Heart Rate (HR)

Baseline heart rate was comparable among the three groups ($F = 0.187$, $p = 0.830$). Following remifentanil administration, heart rate decreased by 7.3%, 16.3%, and 18.6% in Groups R1, R2, and R3, respectively. One minute after tracheal intubation, heart rate increased by 27.5% above baseline in Group R1, whereas Groups R2 and R3 demonstrated attenuation of the response, with values remaining 4.2% and 6.4% below baseline, respectively. The intergroup difference was highly significant at 1 minute ($F = 18.07$, $p = 0.002$), with significant pairwise differences between R1–R2 ($p = 0.001$), R2–R3 ($p = 0.040$), and R1–R3 ($p = 0.001$). Similar significant differences persisted up to 5 minutes after intubation, after which heart rate values became comparable among the groups ($p > 0.05$).

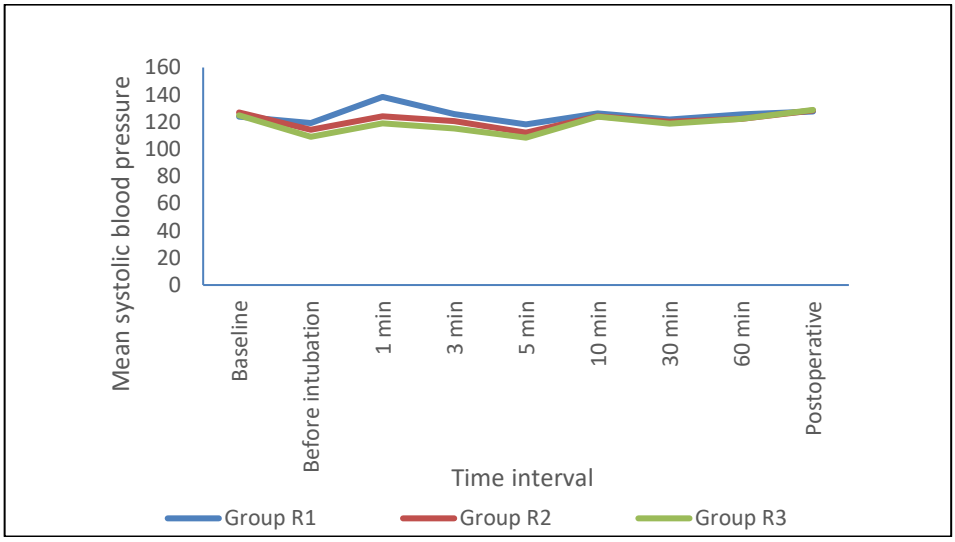
Parameters / Group Variables	Group R1 (0.5 µg/kg)	Group R2 (1.0 µg/kg)	Group R3 (2.0 µg/kg)	p-value
Age (years), Mean ± SD	40.23 ± 11.09	40.73 ± 11.14	40.43 ± 10.41	0.984 (NS)
Gender Distribution (Male/Female), n	15 / 15	15 / 15	19 / 11	0.488 (NS)
ASA Physical Status Grade (I / II), n	13 / 17	15 / 15	17 / 13	0.587 (NS)
Total Body Weight (kg), Mean ± SD	75.10 ± 13.11	74.53 ± 13.84	73.20 ± 13.32	0.854 (NS)
Duration of Surgical Procedure (min), Mean ± SD	82.50 ± 24.31	83.10 ± 22.44	85.83 ± 20.56	0.834 (NS)



Graph 1: Mean Heart Rate (Per Minute)

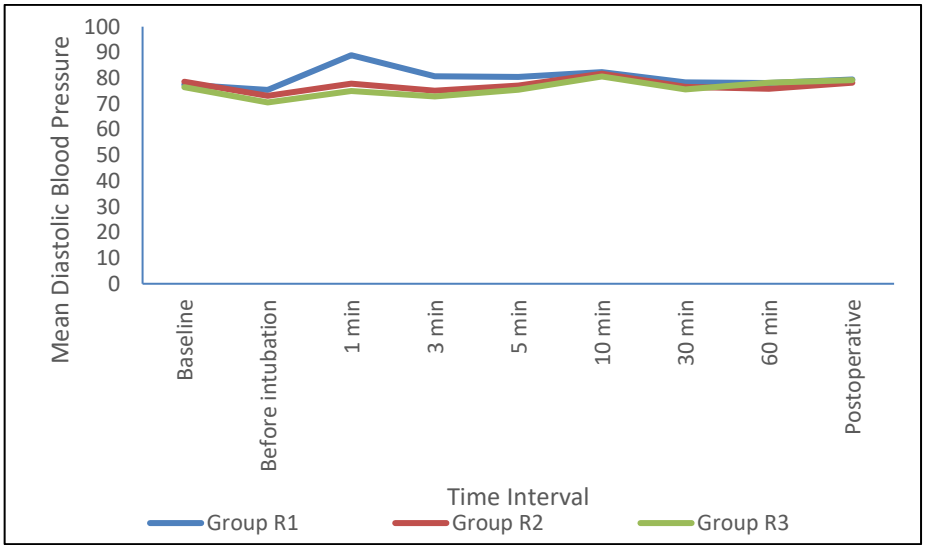
Systolic Blood Pressure (SBP)

Baseline systolic blood pressure was comparable among the groups (F = 0.427, p = 0.654). After remifentanil administration, SBP decreased by 3.8%, 9.8%, and 11.9% in Groups R1, R2, and R3, respectively. Following intubation, SBP increased by 11.7% above baseline in Group R1, while remaining 2.2% below baseline in Group R2 and 4.7% below baseline in Group R3. The intergroup difference at 1 minute was highly significant (F = 27.34, p = 0.002), with significant pairwise differences between R1–R2 (p = 0.001), R2–R3 (p = 0.020), and R1–R3 (p = 0.007). Significant differences persisted for up to 5 minutes post-intubation, after which values returned to baseline and became comparable.



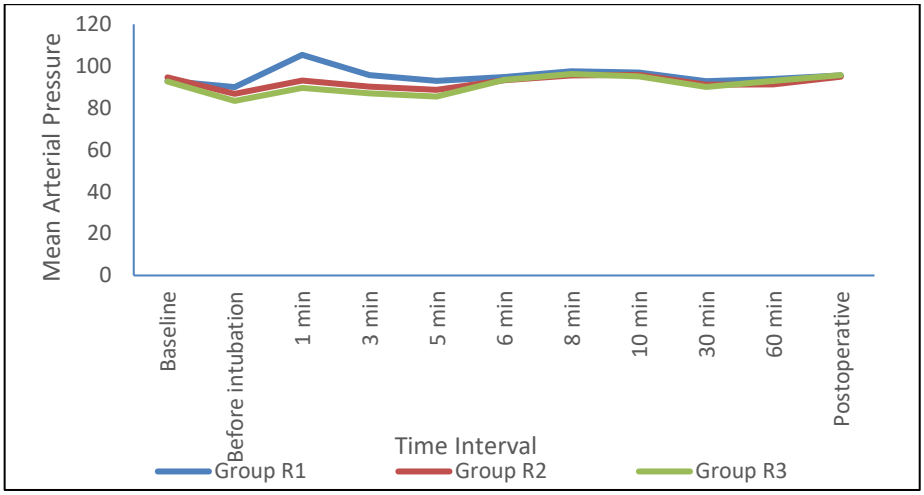
Diastolic Blood Pressure

Baseline DBP values were similar among the groups (F = 0.408, p = 0.666). Remifentanil administration produced reductions of 2.5%, 1.3%, and 2.6% in Groups R1, R2, and R3, respectively. One minute following intubation, DBP increased by 14.8% above baseline in Group R1, whereas values remained close to baseline in Groups R2 and R3. The intergroup difference was highly significant (F = 10.06, p = 0.001), with significant pairwise differences between R1–R2 (p = 0.009) and R1–R3 (p = 0.004). Statistical significance persisted through the first 5 minutes after intubation.



Mean Arterial Pressure (MAP)

Baseline MAP values did not differ significantly among groups (F = 0.451, p = 0.639). Following remifentanil administration, MAP decreased by 2.6%, 3.2%, and 4.6% in Groups R1, R2, and R3, respectively. At 1 minute after intubation, MAP increased by 14.0% above baseline in Group R1, while Groups R2 and R3 remained 1.7% and 3.3% below baseline. This difference was highly significant (F = 9.32, p = 0.002). Significant pairwise differences were observed between R1–R2 (p = 0.003), R2–R3 (p = 0.010), and R1–R3 (p = 0.009). Similar findings persisted up to 5 minutes post-intubation.



DISCUSSION

Direct laryngoscopy and airway handling provoke a marked sympathoadrenal stress response mediated by reflex coordination within the central nervous system.9 Securing the airway can trigger severe hypertension and sinus tachycardia. While well-tolerated in normal individuals, this response poses significant clinical risks for patients with underlying cardiovascular compromise.10 This study evaluated the comparative safety and efficacy of three different bolus doses of remifentanil to identify an optimal dosing approach for clinical use.

Our findings demonstrate a clear, dose-dependent relationship for remifentanil in blunting the pressor response. The lowest dose tested (0.5 µg/kg in Group R1) proved inadequate, as evidenced by a substantial spike in heart rate and blood pressure one minute after intubation. This aligns with findings by O'Hare et al11 and Lee et al,12 who reported that a 0.5 µg/kg bolus dose does not provide sufficient protection against the intense reflex stimulation caused by airway manipulation. Conversely, remifentanil doses of 1.0 µg/kg (Group R2) and 2.0 µg/kg (Group R3) successfully suppressed the post-intubation hypertensive and tachycardia responses, keeping parameters near pre-induction baselines

However, the highest dose (2.0 µg/kg) caused significant cardiovascular depression. Group R3 experienced a 23.33% incidence of systemic hypotension and a 13.33% incidence of sinus bradycardia. This over-suppression reflects enhanced vagal tone and profound inhibition of sympathetic output at higher doses, consistent with reports by Cha et al,13 who noted high rates of hypotension and bradycardia when utilizing larger remifentanil boluses. In contrast, the intermediate dose of 1.0 µg/kg in Group R2 provided highly effective protection against the pressor reflex while maintaining excellent hemodynamic stability and a superior safety profile. Secondary complications , such as chest wall rigidity or postoperative nausea and vomiting, were rare and non-significant across all groups, confirming that a slow bolus injection over 30 to 60 seconds ensures a high margin of safety.

CONCLUSION

In conclusion, this randomized double-blind study demonstrates that remifentanil blunts the haemodynamic pressor response to laryngoscopy and endotracheal intubation in a clear, dose-dependent manner. An intravenous bolus dose of 0.5 µg/kg is insufficient to suppress this reflex response, whereas a dose of 2.0 µg/kg carries a high risk of inducing intraoperative hypotension and bradycardia. Remifentanil administered as an intravenous bolus at a dose of 1.0 µg/kg establishes the ideal clinical balance, providing robust protection against airway stress reflexes while ensuring optimal hemodynamic stability and safety.

Limitation

This study was conducted only in ASA I and II patients, so the findings may not apply to patients with significant cardiovascular disease or a difficult airway. We also did not assess catecholamine or remifentanil plasma levels, which could have provided further insight into the sympathetic response. Since only bolus doses were studied, further research comparing bolus, continuous infusion, and TCI techniques in higher-risk patients would be useful.

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