Section: Anaesthesia

Original Research Article

COMPARATIVE STUDY OF SUBLINGUAL NITROGLYCERINE SPRAY VS INTRAVENOUS FENTANYL AND SUBLINGUAL NITROGLYCERINE SPRAY ON TRACHEAL EXTUBATION RESPONSE-PROSPECTIVE RANDOMIZED STUDY

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Received : 10/10/2025
Received in revised form : 07/12/2025
Accepted : 24/12/2025

Keywords:
Tracheal extubation, Nitroglycerine spray, Fentanyl, General anesthesia, Airway reflex.

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DOI: 10.47009/jamp.2026.8.2.74

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (2); 407-411

ABSTRACT

Background: Tracheal extubation is a critical phase of general anesthesia, often accompanied by hemodynamic disturbances such as tachycardia and hypertension due to sympathetic stimulation. These responses may be detrimental, particularly in patients with cardiovascular or cerebrovascular risk. Pharmacologic strategies to attenuate these responses must be short-acting and non-sedative. Nitroglycerine (NTG), a vasodilator, and fentanyl, a short-acting opioid, are both known to mitigate such responses. The aim is to evaluate and compare the efficacy of intravenous fentanyl (1 µg/kg) combined with sublingual nitroglycerine spray (0.4 mg/puff) versus sublingual nitroglycerine spray alone in attenuating the hemodynamic response during tracheal extubation in normotensive patients undergoing elective surgeries. **Materials and Methods:** This was a prospective, single-blind, randomized controlled trial conducted at a tertiary care hospital between January 2021 and July 2022, including 100 ASA I and II normotensive patients aged 20–60 years undergoing elective surgery under general anesthesia. Patients were randomized into two groups of 50 each: Group I received IV fentanyl plus NTG spray; Group II received NTG spray alone. Hemodynamic parameters (HR, SBP, DBP, MAP) were measured at baseline, reversal (Tr), extubation (Tex), and at 1, 3, 5, 10, and 20 minutes post-extubation. Statistical analysis was performed using SPSS v25 and Epi Info v7.3, with $p < 0.05$ considered significant. **Result:** The two groups were comparable in terms of age, gender, and ASA status. Heart rate was significantly lower in the NTG-only group at all measured intervals post-extubation ($p < 0.05$). Systolic blood pressure was significantly lower in the NTG + Fentanyl group at reversal, extubation, and 20 minutes post-extubation. Diastolic blood pressure and mean arterial pressure were also significantly lower in the NTG + Fentanyl group at most time points, indicating a more consistent attenuation of the pressor response. No severe complications or adverse events were reported in either group. **Conclusion:** A combination of intravenous fentanyl (1 µg/kg) and sublingual nitroglycerine spray (0.4 mg) administered before extubation provides superior attenuation of hemodynamic responses and airway reflexes compared to nitroglycerine alone, facilitating smoother and safer tracheal extubation in normotensive patients.

INTRODUCTION

Tracheal extubation is a critical phase of general anesthesia, just as important as intubation. It involves removing the endotracheal tube through the mouth or nose after ensuring the patient has adequate respiratory effort and muscle strength. However, this process can trigger airway irritation, coughing, anxiety, and haemodynamic disturbances due to sympathetic discharge from laryngeal and pharyngeal stimulation. These responses include increased heart rate, blood pressure, and even arrhythmias —especially harmful in patients with cardiovascular or cerebrovascular conditions.[1-3] Respiratory complications like coughing, laryngospasm, and bronchospasm are notably more frequent during extubation than intubation and can

elevate intracranial, intraocular, or intraabdominal pressures, posing risks for high-risk patients.[4]

Given the potential dangers, smooth extubation—marked by the absence of coughing, straining, or breath-holding—is a priority for anesthesiologists.[5,6] While many pharmacologic agents like lignocaine, esmolol, diltiazem, labetalol, fentanyl, and propofol have proven effective during intubation, their use during extubation is limited. Drugs used at this stage must be short-acting, non-sedative, and non-respiratory depressants. Some intravenous agents like lignocaine, esmolol, and diltiazem meet these criteria. Non-pharmacological approaches like the Bailey manoeuvre aim to minimize airway reflexes, but no method has achieved universal success in completely suppressing haemodynamic responses during extubation.[11-18]

Nitroglycerine (NTG), due to its vasodilatory properties, is sometimes employed to blunt blood pressure surges during extubation. It generates nitric oxide, relaxing vascular and bronchial smooth muscles, which may also help prevent laryngospasm. NTG is particularly advantageous because it lowers blood pressure without compromising cardiac output, simultaneously improving coronary perfusion and reducing myocardial oxygen demand. Fentanyl, a short-acting opioid, can also attenuate cardiovascular and airway reflexes by enhancing parasympathetic tone and suppressing the stress response. Administered in low doses (1 µg/kg), it effectively minimizes haemodynamic disturbances without prolonging recovery or causing significant side effects.[19,20]

The present study aims to evaluate and compare the efficacy of intravenous fentanyl (1 µg/kg) combined with one puff of sublingual nitroglycerine spray (0.4 mg/puff) versus sublingual nitroglycerine spray (0.4 mg/puff) alone in attenuating the haemodynamic response during tracheal extubation in normotensive patients undergoing elective surgeries. The primary objective is to observe and assess changes in haemodynamic parameters such as systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate during tracheal extubation. Secondary objectives include evaluating the occurrence of postoperative complications such as sore throat, laryngospasm, and aspiration, determining the effectiveness of timing in the administration of sublingual nitroglycerin spray and intravenous fentanyl, and documenting the incidence of side effects and overall safety of both drugs.

MATERIALS AND METHODS

This was a prospective, single-blind, randomized controlled trial conducted at a tertiary care hospital between January 2021 and July 2022. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment. Patients were blinded to group allocation. A total of 100 normotensive patients, aged 20 to 60 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for elective surgeries under general anesthesia requiring tracheal intubation were included. The sample size was calculated based on prior studies (Binod Pegu et al.17) using a power of 80% and an alpha of 0.05 to detect differences in hemodynamic parameters at 1, 3, and 5 minutes post-extubation.

Inclusion Criteria

- ASA physical status I and II
- Age between 20–60 years
- Body weight 40–80 kg
- Normotensive status
- Undergoing elective surgery under general anesthesia with tracheal intubation

Exclusion Criteria

- ASA physical status III, IV, or V
- Preexisting hemodynamic instability
- Bleeding disorders
- Use of vasodilators (e.g., sildenafil)
- Requirement of postoperative ventilatory support
- Pregnant or lactating women

Randomization and Group Allocation

Patients were randomized into two groups using the chit-box method:

- Group I (n = 50): Received intravenous fentanyl (1 µg/kg) and one puff of sublingual nitroglycerine spray (0.4 mg/puff)
- Group II (n = 50): Received only one puff of sublingual nitroglycerine spray (0.4 mg/puff)

Preoperative Preparation and Anesthesia Protocol: All patients underwent a detailed pre-anesthetic evaluation and routine investigations. Fasting guidelines included 6 hours for solids, 4 hours for semi-solids, and 2 hours for clear fluids. In the operating room, standard monitors were attached to measure heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2), and electrocardiogram (ECG). Intravenous access was secured. Premedication included IV glycopyrrolate 0.004 mg/kg, IV midazolam 0.02 mg/kg, and IV fentanyl 2 µg/kg. Anesthesia was induced with IV propofol 2 mg/kg and IV vecuronium 0.08 mg/kg to facilitate intubation. Intubation was performed under direct laryngoscopy using an appropriately sized, lubricated, cuffed, disposable endotracheal tube. Anesthesia was maintained with O_2, N_2O, isoflurane, and intermittent doses of vecuronium.

Intervention and Data Collection: At the conclusion of surgery, inhalational agents were tapered, and once spontaneous respiration resumed, Group I received IV fentanyl (1 µg/kg) followed by sublingual nitroglycerine spray (0.4 mg), while Group II received sublingual nitroglycerine spray alone. Neuromuscular blockade was reversed with IV glycopyrrolate 0.008 mg/kg and IV neostigmine 0.06 mg/kg. Hemodynamic parameters (HR, SBP, DBP, MAP, SpO_2) were recorded every minute during and after extubation at 1, 3, 5, 10, and 20 minutes.

Postoperative Monitoring and Safety Assessment: Patients were monitored for complications including

ISSN (O): 2687-5365; ISSN (P): 2753-6556

hypotension (SBP drop ≥20% from baseline), bradycardia (HR drop ≥20%), tachycardia, ECG changes (ST-T changes or arrhythmias), headache, laryngospasm, sore throat, aspiration, and respiratory depression. Interventions for hemodynamic instability included IV ephedrine 6 mg for hypotension and IV atropine 0.6 mg for bradycardia.

Statistical Analysis: Data entry was performed using Microsoft Excel, and statistical analysis was carried out using SPSS version 25.0 (IBM Corp., Armonk, NY) and Epi Info version 7.3 (CDC, Atlanta, GA). Descriptive statistics were used to summarize demographic, clinical, and intraoperative variables. Categorical variables were expressed as frequencies and percentages, and comparisons between groups were made using the Chi-square test. Continuous variables were presented as mean ± standard deviation (SD), and intergroup comparisons were conducted using the independent Student's t-test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The present study had enrolled 100 patients of ASA I and II between age group 18-60 years were randomized to two groups having 50 patients in each group. Table 1 shows the distribution of age, gender, and ASA status among the study participants. In the NTG + Fentanyl group, the majority of patients, 17 (34%), were in the 30–39 years age group, followed by 14 (28%) in the 40–49 years group and 10 (20%) in the 50–59 years group. In the NTG group, most patients, 20 (40%), were also in the 30–39 years age group, followed by 8 (16%) each in the 20–29 and ≥60 years categories. Regarding gender, the NTG + Fentanyl group consisted of 27 (54%) males and 23 (46%) females, whereas the NTG group had a higher proportion of males, with 35 (70%) male and 15 (30%) female patients. ASA status distribution revealed that in the NTG + Fentanyl group, 26 patients (52%) were ASA class I and 24 (48%) were ASA class II. In contrast, the NTG group had 34 patients (68%) with ASA I status and 16 (32%) with ASA II status.

[Table 2] presents the comparison of hemodynamic variables—heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP)—between the two groups at various intervals. A statistically significant difference ($p < 0.05$) was observed in heart rate at all-time points, with consistently higher values in the NTG + Fentanyl group compared to the NTG-only group. Systolic blood pressure was significantly lower in the NTG + Fentanyl group at Tr (reversal), Tex (extubation), and at 20 minutes post-extubation. Although differences in SBP at 1, 3, and 5 minutes were not consistently significant, the trend favored a more stable profile in the NTG group. Diastolic blood pressure was significantly lower in the NTG + Fentanyl group at most intervals except at reversal (Tr), where there was no statistical difference. Mean arterial pressure showed significantly lower values in the NTG + Fentanyl group from the time of extubation through the 20-minute mark, indicating a more attenuated hemodynamic response compared to the NTG-only group.

Table 1: Demographic and Clinical Profile of Study Participants (N = 100)

Variable	Category	NTG + Fentanyl Group (n = 50)	NTG Group (n = 50)
Age Group (years)	20–29	6 (12%)	8 (16%)
	30–39	17 (34%)	20 (40%)
	40–49	14 (28%)	7 (14%)
	50–59	10 (20%)	7 (14%)
	≥60	3 (6%)	8 (16%)
Gender	Male	27 (54%)	35 (70%)
	Female	23 (46%)	15 (30%)
ASA Status	ASA I	26 (52%)	34 (68%)
	ASA II	24 (48%)	16 (32%)

Table 2: Comparison of study subjects according to study variables at different intervals in both groups

Study variable		Baseline	Tr (at time of reversal)	Tex (at time of extubation)	1-Min	3-Min	5-Min	20-Min
Heart rate (per minute)	NTG + Fentanyl (N= 50)	79.32+10.51	84.80+9.57	87.90+9.47	90.48+ 9.84	98.52+ 9.78	109.24+ 8.50	116.36+ 7.12
	NTG only (N= 50)	81.46+9.55	73.56+9.22	81.22+9.65	84.08+ 9.26	79.68+ 7.10	76.88+ 8.22	74.68+ 7.10
	t test p value	0.0001	0.0001	0.0007	0.001	0.0001	0.0001	0.0001
systolic blood pressure (mm/Hg)	NTG + Fentanyl (N= 50)	129.50+17.96	120.04+12.25	124.28+10.10	126.78+ 11.27	122.14+ 12.50	116.36+ 6.93	129.50+ 17.96
	NTG only (N= 50)	128.72+8.55	111.20+11.05	129.44+8.11	126.96+ 3.57	120.76+ 8.26	119.04+ 13.66	117.28+ 13.50
	t test p value	0.77	0.0002	0.005	0.05	0.5	0.21	0.0002
diastolic blood pressure (mm/Hg)	NTG + Fentanyl (N= 50)	129.50+17.96	74.62+10.22	78.88+8.04	72.16+ 10.43	69.20+ 9.95	66.14+ 9.31	66.30+ 8.27
	NTG only (N= 50)	83.00+5.69	74.60+7.67	87.38+7.40	84.92+ 9.10	81.52+ 9.54	74.48+ 5.93	77.08+8.12
	t test p value	0.0001	0.99	0.0001	0.0001	0.0001	0.0001	0.0001

ISSN (O): 2687-5365; ISSN (P): 2753-6556

mean arterial pressure (mm/Hg)	NTG + Fentanyl (N= 50)	96.51+9.58	89.76+9.77	94.01+7.53	90.36+ 9.34	86.84+ 9.28	82.88+ 6.62	82.30+ 7.72
	NTG only (N= 50)	98.24+5.88	86.80+5.35	101.40+5.82	98.93+ 6.23	94.60+ 7.30	92.00+ 6.91	90.48+ 5.55
	t test p value	0.28	0.06	0.0001	0.0001	0.0001	0.0001	0.0001

DISCUSSION

Tracheal extubation triggers significant cardiovascular changes due to reflex sympathetic stimulation, often resulting in tachycardia and elevated mean arterial pressure. This study compared the efficacy of sublingual nitroglycerin alone versus in combination with intravenous fentanyl in attenuating such responses. Demographic profiles were comparable between groups, with most patients in the 30–39 age range and a predominance of ASA I status, consistent with findings from Pegu et al,[17] Raikwar et al,[18] and Tagalpallewar et al.[19]

Regarding heart rate, the NTG-only group demonstrated a progressive decline post-extubation, while the NTG + Fentanyl group showed a sustained rise. This pattern differed from findings by Pegu et al,[17] and Vyas et al,[20] who observed better heart rate control with NTG + Fentanyl during intubation, possibly due to study timing differences (intubation vs. extubation). Prior studies by Kumari et al,[21] and Fassoulaki et al,[22] also highlight the reflex tachycardia induced by nitroglycerin's vasodilatory effect, supporting the current findings. For systolic and diastolic blood pressures, the NTG + Fentanyl group showed significantly lower values at key time points, especially at reversal, extubation, and up to 20 minutes post-extubation. These results align with Pegu et al,[17] Kumari et al,[21] and Raikwar et al,[18] all of whom observed improved hemodynamic control with combination therapy. In contrast, Channaiah et al,[23] reported peak SBP differences at 7 minutes post-intubation, emphasizing the time-dependent effects of intervention.

Mean arterial pressure (MAP) was significantly lower in the NTG + Fentanyl group at extubation and all subsequent time intervals. Similar observations were made by Pegu et al,[17] while Channaiah et al,[23] noted intervals where MAP differences were not statistically significant. The findings by Gamze Kucukosman et al,[24] also reinforce the role of NTG in limiting extubation-related pressor responses, particularly in the first five minutes.

Overall, the combination of IV fentanyl with sublingual NTG provided superior attenuation of extubation-induced hemodynamic fluctuations compared to NTG alone. This supports the strategy of multimodal attenuation, particularly in normotensive patients undergoing elective surgeries under general anesthesia.

CONCLUSION

From the data and statistical analysis, we conclude that, Combination of single puff of sub-lingual nitroglycerine spray(0.4mg/puff) + IV fentanyl (1microgram/kg) before extubation attenuates haemodynamic stress response and airway reflex to a better extent as compared to single puff of sublingual nitroglycerine spray(0.4mg/puff) allowing smooth and easy tracheal extubation.

Limitations

The present study had a few limitations. It was conducted on a relatively small sample size of 50 patients per group. Only ASA I and II patients were included, excluding those with ASA III and above or with comorbidities like coronary artery disease, hypertension, and diabetes, who may experience greater variations in heart rate and mean blood pressure during extubation. Airway reflexes were evaluated only at the time of extubation, while a longer postoperative observation could have captured delayed respiratory complications. Although invasive arterial blood pressure monitoring offers greater accuracy, it was not used, as the procedures performed did not justify such intervention. Stress mediators released during extubation were not measured, which could have provided additional insight into the effects of the study drugs. Finally, factors like endotracheal tube cuff pressure, tube diameter, and any requirement for postoperative re-intubation were not recorded, which may have influenced the outcomes.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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