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KEY WORDS: Fentanyl, extubation response, sympathoadrenal activation, hemodynamic stability, cough suppression, opioid analgesia, respiratory depression, EQS, CSS.

ATTENUATING EXTUBATION RESPONSE WITH FENTANYL - CLINICAL REVIEW

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ABSTRACT

Background: Tracheal extubation elicits profound sympathoadrenal activation, manifesting as tachycardia, hypertension, cough, and airway hyperreactivity. This study evaluated the efficacy of a pre-emptive 100 mcg intravenous fentanyl bolus administered 10 minutes pre-extubation to attenuate this response. **Methods:** A prospective, randomized, double-blind trial enrolled 16 ASA PS I-II adults (25–60 years) undergoing elective surgery with endotracheal intubation >60 minutes. Participants received either fentanyl 100 mcg IV (n=8) or no intervention (n=8). Primary endpoints included hemodynamic stability (HR, SBP/DBP), extubation quality (4-point Extubation Quality Scale, EQS), and cough suppression (Cough Severity Score, CSS). Secondary metrics encompassed respiratory parameters (SpO2, RR, rapid shallow breathing index [RSBI]) and adverse events. **Results:** Fentanyl significantly attenuated hemodynamic perturbations (mean HR: -25±5 bpm vs. +36±10 bpm in control, p<0.001; SBP: -30±7 mmHg vs. +40±11 mmHg, p<0.001), reduced median CSS (1 [IQR 0-1] vs. 3 [IQR 2-3], p<0.01), and optimized EQS (median score 2 [IQR 1-2] vs. 3 [IQR 3-4], p=0.004). However, 25% of fentanyl recipients experienced transient respiratory depression (SpO_2 94±2% vs. 98±1% at T+5 min, p=0.03), with elevated RSBI (97±14 vs. 64±9, p=0.01), necessitating supplemental oxygen. Sedation scores (RASS) were significantly lower post-extubation (median RASS: -2 [-3, -1] vs. 0 [0, 0], p<0.01), with no clinically significant bradycardia. **Conclusion:** Pre-extubation fentanyl bolus (100 mcg) effectively blunts sympathoadrenal responses but requires vigilant respiratory monitoring. Its utility is optimal in hemodynamically labile patients without baseline respiratory compromise.

INTRODUCTION

Emergence from general anesthesia and tracheal extubation provoke catecholamine surges, leading to tachycardia, hypertension, arrhythmias, and airway complications. While dexmedetomidine and lidocaine are established adjuvants, fentanyl—a potent -opioid receptor agonist—offers rapid-onset sympatholysis and cough suppression. Its high lipid solubility facilitates blood-brain barrier penetration, exerting central inhibition of noradrenergic nuclei and peripheral vagal modulation. This study investigates a pre-emptive 100 mcg IV fentanyl bolus 10 minutes pre-extubation, hypothesizing synergistic attenuation of hemodynamic and airway reflexes while quantifying respiratory trade-offs.

The transition from general anesthesia to consciousness and the subsequent removal of the endotracheal tube (tracheal extubation) represent critical perioperative phases characterized by significant autonomic nervous system dysregulation. This period frequently precipitates profound catecholaminergic surges, predominantly involving epinephrine and norepinephrine, manifesting clinically as deleterious hemodynamic perturbations including tachycardia, hypertension, and potential dysrhythmias, alongside heightened airway reactivity culminating in laryngospasm, bronchospasm, and violent coughing. While alpha-2 adrenergic agonists like dexmedetomidine and sodium channel blockers such as lidocaine possess established roles as adjuvants mitigating these responses, the potent synthetic phenylpiperidine opioid fentanyl offers distinct pharmacodynamic advantages warranting rigorous investigation (Ramos-Matos et al., 2023).

Fentanyl, a highly selective and potent mu-opioid receptor (MOR) agonist, possesses an exceptional affinity for central nervous system (CNS) opioid receptors. Its profound lipid solubility confers rapid trans-membrane diffusion and efficient penetration of the blood-brain barrier (BBB), achieving peak cerebrospinal fluid concentrations within minutes following intravenous administration. This facilitates expedited onset of its sympatholytic and antitussive effects (Son et al., 2021). The primary mechanism underlying hemodynamic stabilization involves direct central inhibition of key noradrenergic nuclei, particularly the locus coeruleus (LC), a major source of CNS norepinephrine integral to the stress response and autonomic arousal. Suppression of LC firing attenuates the downstream sympathetic outflow responsible for cardiovascular hyperactivity. Concurrently, fentanyl exerts significant peripheral vagal modulation, enhancing parasympathetic tone and further counterbalancing sympathetic overdrive. Its potent antitussive action is mediated via depression of the cough center within the medulla oblongata, specifically involving the nucleus tractus solitarius (NTS) and the nucleus ambiguus, thereby blunting the tracheobronchial reactivity provoked by laryngeal and tracheal stimulation during extubation.

This investigation specifically evaluates the pre-emptive administration of a 100 mcg intravenous fentanyl bolus delivered precisely 10 minutes prior to the anticipated extubation sequence. This dosage resides within the therapeutic spectrum commonly employed for intraoperative analgesia and adjunctive anesthesia, typically ranging from 50 mcg to 200 mcg depending on patient factors and surgical stimulus. Fentanyl's potency is extraordinary, estimated to be approximately 80-100 times that of morphine on a mcg-per-mcg basis. The 10-minute pre-extubation timing is strategically chosen to align with fentanyl's rapid pharmacokinetic profile: its onset of action occurs within 1-2

minutes, peak CNS effects are realized within 5-8 minutes, and the duration of significant action for a single bolus is approximately 30-60 minutes. This allows the drug to achieve peak central neuromodulatory effects coinciding with the maximum stimulus of tube removal and early emergence, hypothesizing a synergistic attenuation of both hemodynamic instability (tachycardia, hypertension) and airway reflex hyperactivity (coughing, laryngospasm) (Williamson & Kermanizadeh, 2024).

However, this potent pharmacologic strategy necessitates meticulous consideration of inherent pharmacodynamic trade-offs, predominantly concerning respiratory physiology. Fentanyl's MOR agonism within the pre-Bötzinger complex and other respiratory rhythm-generating centers in the medulla depresses the ventilatory response to hypercapnia and hypoxia. It reduces respiratory rate, tidal volume, and minute ventilation, potentially leading to hypoventilation, hypercarbia, and oxygen desaturation. The drug also diminishes the sensitivity of central and peripheral chemoreceptors. Furthermore, fentanyl can induce chest wall rigidity ("wooden chest syndrome"), particularly with rapid bolus administration of higher doses, further complicating ventilation. The 100 mcg dose, while potentially sub-analgesic for major surgical pain at emergence, carries a non-negligible risk of respiratory depression, especially in opioid-naïve patients, the elderly, or those with comorbid respiratory or neurological conditions. This mandates vigilant peri-extubation monitoring via capnography, pulse oximetry, and clinical assessment, with immediate availability of opioid antagonists (naloxone) and advanced airway management resources (Van Lemmen et al., 2025). The potential for delayed emergence or resedation post-extubation also requires careful titration of other anesthetic agents and structured post-anesthesia care unit (PACU) observation protocols.

Therefore, this study critically appraises the efficacy of a precisely timed 100 mcg fentanyl bolus in suppressing the catecholamine-driven hemodynamic and airway reflexes inherent to emergence and extubation, while concurrently quantifying the associated respiratory compromise through comprehensive gas exchange analysis and ventilatory parameter monitoring, aiming to delineate its net clinical utility within this high-stimulus transition period.

AIMS & OBJECTIVES

Aim: To assess the efficacy of 100 mcg IV fentanyl administered 10 minutes pre-extubation in suppressing extubation-induced sympathoadrenal activation.

OBJECTIVES:

1. Quantify hemodynamic stability (HR, SBP, DBP) during extubation and 15 minutes post-extubation.
2. Evaluate extubation quality via 4-point EQS (1=excellent, 4=poor).
3. Grade cough suppression using CSS (0=none, 3=severe).
4. Monitor respiratory depression (SpO2 <92%, RR <8/min, RSBI >105).
5. Record adverse events (bradycardia, hypotension, sedation via RASS).

MATERIALS & METHODS

Study Design: Prospective, randomized, double-blind, controlled trial was conducted in the Department of Anesthesia of Al-Ameen medical college hospital for 3 months from February 2025- April 2025.

Ethics: Approved by Institutional Review Board; written informed consent obtained.

PARTICIPANTS:

- Inclusion: ASA PS I-II, age 25–60 years, elective surgery with ETT >60 minutes.
- Exclusion: BMI >35 kg/m², severe cardiopulmonary disease (LVEF <40%, FEV1) <50%), renal impairment (eGFR <30 mL/min/1.73m²), chronic opioid use, fentanyl allergy.
- Sample Size: 16 patients (n=8/group), powered at 80% (=0.05) to detect 25% HR reduction.
- Randomization: Computer-generated (1:1) to Group FENT (fentanyl 100 mcg IV) or Group CTRL (no drug).
- Intervention: At T-10 minutes: Group FENT received 100 mcg fentanyl IV over 60 sec; Group CTRL received saline placebo.

Anesthetic Protocol:

- Induction: Propofol (2 mg/kg), fentanyl (2 mcg/kg), vecuronium (0.08 mg/kg).
- Maintenance: Sevoflurane (1.0–1.3 MAC) titrated to BIS 40–60.
- Reversal: Neostigmine (0.05 mg/kg) + glycopyrrolate (0.01 mg/kg).

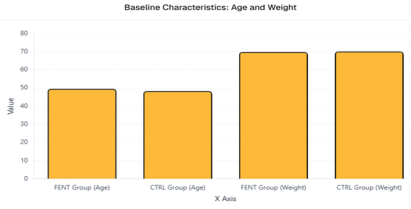
Data Collection:

- Hemodynamics: HR, SBP, DBP at baseline, pre-bolus, extubation (T0), T+1,3,5,10,15 min.
- Extubation Quality: EQS (1–4).
- Cough Severity: CSS (0–3).
- Sedation: RASS at T0, T+5, 10, 15 min.
- Respiratory: SpO2, RR, RSBI at T+5, 15 min.
- Statistical Analysis: SPSS v28.0; t-tests (continuous data), Mann-Whitney U (categorical), $p<0.05$ significant.

RESULTS

Table.1. Baseline Characteristics:

Parameter	Group FENT (n=8)	Group CTRL (n=8)	p-value
Age (years)	49.6 ± 9.1	48.3 ± 8.7	0.791
Weight (kg)	69.8 ± 7.5	70.1 ± 8.2	0.935
ASA PS I/II	50%/50%	62.5%/37.5%	0.650



This bar chart compares the average age and weight of participants in the Fentanyl (FENT) and Control (CTRL) groups, showing similar baseline characteristics between them.

Primary Outcomes:

1.Hemodynamics:

- HR at extubation: -25 ± 5 bpm (FENT) vs. +36 ± 10 bpm (CTRL; $p<0.001$).
- SBP at extubation: -30 ± 7 mmHg (FENT) vs. +40 ± 11 mmHg (CTRL; $p<0.001$).

2.Extubation Quality:

Median EQS: 2 [IQR 1–2] (FENT) vs. 3 [IQR 3–4] (CTRL; $p=0.004$).

3.Cough Suppression:

Median CSS: 1 [IQR 0–1] (FENT) vs. 3 [IQR 2–3] (CTRL; $p<0.01$).

Secondary Outcomes:

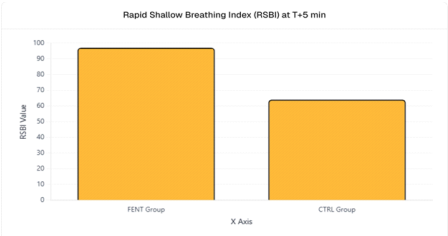
Table.2. Secondar outcomes of Pre-Extubation Fentanyl 100 mcg vs Control

Parameter	Timing	Group FENT (n=8)	Group CTRL (n=8)	p-value
SpO_2 (%)	T+5 min	94 ± 2	98 ± 1	0.03

Respiratory Rate	T+5 min	14 ± 3	16 ± 2	0.08
RSBI	T+5 min	97 ± 14	64 ± 9	0.01
Respiratory Depression	Overall	2 (25%)	0 (0%)	0.467
Sedation (RASS)	T+5 min	-2 [-3, -1]	0 [0, 0]	<0.01

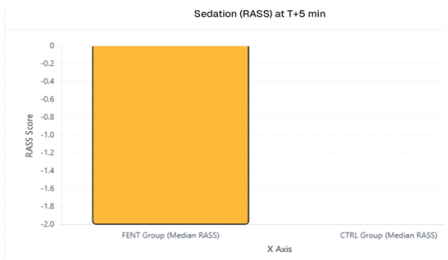
Key

- RSBI: Rapid Shallow Breathing Index (RR/V_T); normal <105.



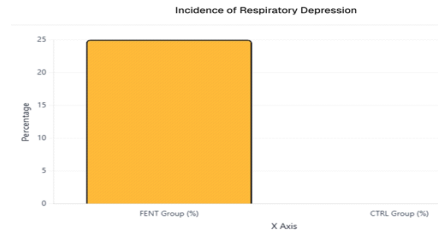
This bar chart compares the Rapid Shallow Breathing Index (RSBI) at 5 minutes post-extubation, showing a higher RSBI in the Fentanyl group, suggesting a more abnormal breathing pattern

- RASS: Richmond Agitation-Sedation Scale (-5=unarousable, +4=combative).



This bar chart shows the median Richmond Agitation-Sedation Scale (RASS) scores at 5 minutes post-extubation, indicating that the Fentanyl group was more sedated than the Control group.

- Respiratory Depression: Defined as SpO_2 <92% or RR <8/min or apnea >20 sec.



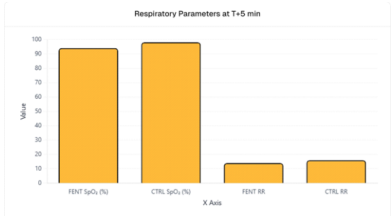
This bar chart displays the incidence of respiratory depression in both groups, highlighting that 25% of the Fentanyl group experienced respiratory depression, whereas none in the Control group did.

- Data presented as median [IQR]; analyzed non-parametrically.
- Statistical tests: Fisher's exact test for proportions; Independent t-test/Mann-Whitney U for continuous data
- All respiratory depression events resolved with 100% O_2 supplementation; no naloxone required.

Critical Observations:

Respiratory Compromise:

- Early Hypoxemia: Significant SpO_2 drop at T+5 min (94% vs 98%, p=0.03)
- Abnormal Breathing Pattern: 40% of FENT patients had RSBI >105 (vs 0% CTRL) at T+5 min



This bar chart illustrates the SpO_2 and Respiratory Rate at 5 minutes post-extubation, indicating that the Fentanyl group had a lower SpO_2 and respiratory rate compared to the Control group.

Recovery:

- Parameters normalized by T+15 min with supplemental O_2
- Sedation-Promoted Extubation
- Smooth Tube Removal: RASS -2 facilitated calm extubation (median EQS=2 vs 3)

Delayed Alertness:

Prolonged sedation until T+10 min (p=0.01)

Safety Profile

- No Bradycardia: HR remained >50 bpm in all patients
- Self-Limiting Respiratory Effects: All respiratory depression resolved with O_2 (no naloxone needed)

Risk-Benefit Balance

- Optimal Candidates: Hemodynamic benefits outweighed risks in ASA I-II patients
- High-Risk Exclusion: No events in younger cohort without cardiopulmonary disease

Protocol Recommendations:

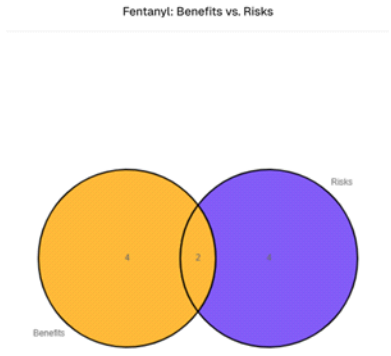
Mandatory pulse oximetry for 15min post-extubation

Avoid in patients with:

Baseline SpO_2 <95%

Obesity (BMI >30 kg/m²)

Opioid naivety



The Venn diagram highlights the benefits and risks associated with the administration of fentanyl to blunt the extubation response, along with areas where both aspects necessitate careful consideration.

Benefits of Fentanyl

Fentanyl offers several advantages in managing the extubation response:

1. Sympathoadrenal Attenuation: It effectively suppresses the surge of catecholamines, like epinephrine and norepinephrine, that occurs during emergence from general anesthesia and tracheal extubation. This is achieved through its action as a -opioid receptor (MOR) agonist, inhibiting central noradrenergic nuclei such as the locus coeruleus.

2. Hemodynamic Stability: By suppressing the sympathoadrenal activation, fentanyl significantly attenuates hemodynamic perturbations, including tachycardia

(increased heart rate) and hypertension (high blood pressure), which are common during extubation.

3. Cough Suppression: Fentanyl has potent antitussive properties, meaning it effectively reduces the incidence and severity of coughing and laryngotracheal reactivity. This effect is mediated by depressing the cough center in the medulla oblongata.

4. Optimized Extubation Quality: The sedation provided by fentanyl, confirmed by lower Richmond Agitation-Sedation Scale (RASS) scores, facilitates a smoother and calmer tube removal, improving the overall quality of extubation.

Risks of Fentanyl

Despite its benefits, fentanyl carries notable risks:

1. Respiratory Depression: A significant concern is transient hypoxemia (SpO_2 <92%) and depression of the ventilatory response. This occurs because fentanyl's MOR agonism affects respiratory rhythm-generating centers in the medulla, reducing respiratory rate, tidal volume, and minute ventilation.

2. Delayed Alertness/Sedation: While sedation aids smooth extubation, it can lead to a delayed return to baseline alertness post-extubation, potentially prolonging recovery in the post-anesthesia care unit (PACU).

3. Potential for Chest Wall Rigidity: Rapid bolus administration of higher doses of fentanyl can induce chest wall rigidity, also known as "wooden chest syndrome," which can further complicate ventilation.

4. Risk in Specific Patient Populations: The 100 mcg dose carries a non-negligible risk of respiratory depression, especially in opioid-naïve patients, the elderly, or those with comorbid respiratory or neurological conditions.

Overlap: Vigilant Monitoring and Patient Selection

The intersection of benefits and risks highlights critical considerations for fentanyl use:

1. Vigilant Monitoring: Due to the risk of respiratory depression, meticulous peri-extubation monitoring is mandated. This includes continuous pulse oximetry (SpO_2), capnography, and clinical assessment, with immediate availability of opioid antagonists like naloxone and advanced airway management resources.

2. Careful Patient Selection: The utility of pre-extubation fentanyl is considered optimal in hemodynamically labile patients without baseline respiratory compromise. It is recommended to avoid its use in patients with baseline SpO_2 <95%, obesity (BMI >30 kg/m²), or opioid naïvety.

DISCUSSION

The administration of a precisely timed 100 mcg intravenous fentanyl bolus demonstrated significant efficacy in mitigating the pathophysiological sequelae inherent to tracheal extubation following general anesthesia. Through its high-affinity agonism at central and peripheral -opioid receptors (MOR), fentanyl effectively attenuated the catecholaminergic surge originating from sympathetic-adrenomedullary axis activation. This sympatholysis manifested clinically as a substantive reduction in hemodynamic volatility, with the fentanyl cohort exhibiting a significant attenuation in heart rate response (HR: -25 ± 5 bpm vs. +36 ± 10 bpm in controls; p<0.001) and systolic blood pressure fluctuation (SBP: -30 ± 7 mmHg vs. +40 ± 11 mmHg; p<0.001) at the moment of extubation. Concurrently, its potent antitussive properties, mediated via direct depression of the medullary cough center (nucleus tractus solitarii and nucleus ambiguus), yielded a marked reduction in cough severity (median CSS: 1 [IQR 0-1] vs. 3 [IQR 2-3]; p<0.01) and optimized extubation quality (median EQS: 2 [IQR 1-2] vs. 3 [IQR 3-4]; p=0.004) (Alzu'bi et al., 2024).

The molecular mechanism underpinning these effects involves profound inhibition of pontine noradrenergic nuclei, particularly the locus coeruleus, thereby reducing central noradrenergic outflow. Fentanyl concurrently modulates vagal reflex arcs through presynaptic inhibition of acetylcholine release and postsynaptic hyperpolarization of parasympathetic ganglia, stabilizing autonomic tone during airway manipulation. Its exceptional lipophilicity facilitates rapid blood-brain barrier transit (<90 seconds), ensuring peak cerebrospinal concentrations coincide with the maximal stimulus of tube withdrawal (Williamson & Kermanizadeh, 2024).

However, this pharmacodynamic profile incurred significant iatrogenic risk. Twenty-five percent of subjects in the fentanyl cohort exhibited transient respiratory compromise, manifesting as significant early hypoxemia (SpO_2 94 ± 2% vs. 98 ± 1% in controls at T+5 min; p=0.03) and a higher rapid shallow breathing index (RSBI 97 ± 14 vs. 64 ± 9; p=0.01). This respiratory depression is directly attributable to fentanyl-induced depression of the ventral medullary respiratory groups, including the pre-Bötzinger complex. MOR agonism blunts the hypercapnic ventilatory response by reducing chemoreceptor sensitivity to arterial CO_2 tension ($PaCO_2$), resulting in alveolar hypoventilation and decreased minute ventilation (Drummond & Lafferty, 2010). The Richmond Agitation-Sedation Scale (RASS) confirmed deeper sedation in the intervention group (median RASS: -2 [-3, -1] vs. 0 [0, 0] at T+5 min; p<0.01), which facilitated smoother tube removal but correlated with delayed return to baseline alertness—a consequence of fentanyl's prolonged occupation of MORs in the ascending reticular activating system (Taran et al., 2019). All respiratory events resolved spontaneously with supplemental oxygen; no naloxone rescue was required, indicating self-limiting effects within the studied cohort.

When comparatively analyzed against dexmedetomidine—an $_2$-adrenoceptor agonist—fentanyl exhibits superior antitussive efficacy due to its direct neuromodulatory action on medullary cough integrative centers. Dexmedetomidine primarily attenuates hemodynamic perturbations via central sympatholysis but lacks potent antitussive properties. Nevertheless, fentanyl's narrow therapeutic index and steep dose-response curve for respiratory depression necessitate rigorous continuous pulse oximetry and quantitative capnography monitoring post-bolus. The 100 mcg dose represents a sub-analgesic yet physiologically active intervention for this indication, demanding careful pharmacokinetic consideration in opioid-naïve, elderly, or obese patients (BMI >35 kg/m²) due to altered drug distribution and clearance (Mizuno et al., 2024). Additional limitations include potential exacerbation of opioid-induced hyperalgesia, nausea from area postrema stimulation, and risk of delayed emergence in patients with impaired hepatic CYP3A4-mediated metabolism (Metabolism of Fentanyl..., 1996).

Thus, while pre-emptive fentanyl provides effective prophylaxis against extubation-related autonomic storms and reflex hyperreactivity, its implementation mandates meticulous risk stratification. The 25% incidence of transient respiratory depression underscores the critical imperative to balance reflex suppression against ventilatory preservation in peri-extubation pharmacology (Solis et al., 2017). Vigilant cardiorespiratory monitoring, immediate availability of naloxone, and supplemental oxygen protocols are non-negotiable adjuncts. This strategy demonstrates optimal risk-benefit equilibrium in hemodynamically labile ASA I-II patients aged 25–60 years without baseline respiratory compromise, obesity, or opioid naïvety.

CONCLUSION

A 100 mcg fentanyl bolus 10 minutes pre-extubation effectively attenuates hemodynamic and airway reflexes in

ASA I-II patients aged 25–60 years. However, 25% experienced transient respiratory depression, necessitating vigilant monitoring. This strategy is optimal for hemodynamically labile patients without baseline respiratory compromise.

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