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Clinical Use of Endotracheal Intubation Without Neuromuscular Blockade: The Current Stage of Knowledge

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Endotracheal intubation is a fundamental component of modern airway management in elective and emergency settings. Neuromuscular blocking agents (NMBAs) are commonly used to optimize intubating conditions by facilitating jaw relaxation, improving vocal cord visualization, and reducing airway trauma. However, their administration can be contraindicated or undesirable in specific situations, such as procedures requiring intraoperative neuromonitoring, short-duration surgeries, patients with neuromuscular disorders, or critically ill individuals at risk of prolonged blockade or adverse reactions.

This review examines current evidence regarding the feasibility, effectiveness, and safety of intubation without neuromuscular blockade. Data from randomized trials and meta-analyses indicate that although NMBAs are associated with a higher incidence of optimal intubation conditions and improved first-attempt success rates, their omission does not significantly increase postoperative complications, such as sore throat or hoarseness. The principal concern with NMBA-free techniques remains hemodynamic instability, particularly hypotension and bradycardia, associated with the deeper levels of anesthesia required to suppress airway reflexes.

Alternative strategies include short-acting opioids (remifentanil, alfentanil, fentanyl, and sufentanil), intravenous hypnotics (propofol, ketamine, and etomidate), inhalational agents (sevoflurane), and adjuncts (dexmedetomidine and magnesium sulfate). These agents attenuate sympathetic responses to laryngoscopy while preserving neuromonitoring compatibility. Their distinct pharmacodynamic profiles influence intubation conditions, apnea duration, and cardiovascular stability.

Current evidence supports the feasibility of NMBA-free intubation in carefully selected patients when performed by experienced clinicians. Individualized risk assessment and careful drug titration are essential. Further large-scale studies are needed to establish standardized protocols and define patient populations most likely to benefit from this approach.

Keywords: Intubation • Neuromuscular Blockade • Trachea • Anesthesiology • Intubation, Intratracheal • Neuromuscular Blocking Agents • Hemodynamics • Airway Management • Review

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Introduction

Muscle relaxants are commonly used to optimize tracheal intubation conditions by reducing patients' resistance and facilitating smoother airway access. Neuromuscular blocking agents (NMBAs) inhibit transmission at the neuromuscular junction, inducing muscle relaxation. Their administration during intubation has been associated with a lower incidence of postoperative laryngeal complications, such as sore throat and hoarseness [1,2]. However, the use of NMBAs is either contraindicated or undesirable in the following: (1) procedures requiring intraoperative neuromonitoring, such as thyroid, spinal, neurosurgical, and parotid gland surgeries, and in short-duration operations [1,2]; (2) patients with neuromuscular disorders such as myasthenia gravis [2,3]; (3) patients with history or high risk of NMBA anaphylaxis or severe adverse reaction [4]; (4) very short procedures in which prolonged paralysis is undesirable [5]; (5) when residual weakness would be particularly hazardous or reversal is unreliable or unavailable; and (6) in pediatric inhalational induction with sevoflurane for selected cases [6]. In these cases, alternative intubation strategies must be considered. This includes techniques compatible with neuromuscular monitoring, avoiding interference caused by muscle relaxants [1]. Effective airway management, both intraoperative and postoperative, requires close coordination between anesthesiology, surgery, and critical care teams to prevent complications such as airway obstruction, aspiration, and hypoxemia [7].

The use of intermediate-acting NMBAs can significantly affect the accuracy of neuromonitoring signals [8]. Typically, endotracheal intubation is performed once full muscle paralysis is achieved [9]. However, it remains unclear whether intubation without NMBAs results in inferior outcomes compared with those of standard practices [2].

Additionally, endotracheal intubation triggers significant psychological responses. For instance, it can increase intraocular pressure (IOP), likely due to elevated mean arterial pressure and the subsequent increases in choroidal blood flow [10]. Laryngoscopy and endotracheal intubation are also associated with sympathetic nervous system activation, causing hypertension and tachycardia due to catecholamine release and an increase in the plasma concentration [10]. These hemodynamic responses can exacerbate existing conditions, such as elevated intracranial pressure and cardiac failure with pulmonary edema, and even precipitate cerebral hemorrhage. To manage these effects, a variety of pharmacologic agents are used, including opioid derivatives, local anesthetics, opioids, beta blockers, alpha-2 adrenergic agonists, vasodilators, magnesium, and high concentrations of volatile anesthetics [10,11].

In this article, we review the current state of knowledge regarding endotracheal intubation without neuromuscular blockade and aim to evaluate its effectiveness and safety profile in various clinical contexts. Endotracheal intubation is a critical procedure frequently performed in elective surgeries and emergency settings. The success and safety of intubation depend not only on the operator's skill, but also on the appropriate pharmacological support. This analysis compares the commonly used anesthetic and adjuvant agents with regard to their efficiency, safety, and hemodynamic impact during airway management.

Each medication, ranging from intravenous agents, such as propofol or ketamine, to inhalational anesthetics, such as sevofluarane, as well as adjunctive drugs, such as opioids, has unique pharmacodynamic and pharmacokinetic profiles. Special attention given to the management of cardiovascular responses, airway reflex suppression, and drug interactions is essential to ensure safe induction with minimal complications.

Techniques of Intubation Using NMBAs

The standard approach to endotracheal intubation typically involves the use of NMBAs, which provide favorable intubation conditions and help minimize the risk of airway trauma and related complications. This effect is achieved by blocking neuromuscular transmission at the neuromuscular junction, leading to muscle relaxation via inhibition of acetylcholine binding to its receptors [2].

NMBAs such as succinylcholine and rocuronium are frequently used due to their effectiveness in facilitating rapid and smooth intubation. Their use is also associated with decreased incidence of postoperative laryngeal complications, including sore throat and hoarseness [2].

However, the use of NMBAs is not without risks, and particular drugs differ in their adverse-effect profiles. Succinylcholine (suxamethonium) is associated with hyperkalemia (particularly in patients with burns, denervation injuries, or myopathies), arrhythmias, bradycardia in children (and brady- or tachycardia in adults), malignant hyperthermia triggering, fasciculations, postoperative myalgia, increased intraocular and intragastric pressure, and cytotoxic muscle injury [12,13]. Atracurium can cause histamine release, leading to flushing, hypotension, tachycardia, and bronchospasm, and has been strongly associated with anaphylaxis, respiratory arrest, ventricular fibrillation, and rare reports of hyperglycemia [12-14]. Cisatracurium, while producing less histamine release and fewer cardiovascular effects than atracurium, is still linked to anaphylaxis, bronchospasm, respiratory arrest, hypotension, and ventricular fibrillation and has shown a pharmacovigilance signal for hepatocellular injury [12,14]. Among aminosteroid agents, rocuronium is notably associated with anaphylaxis, bronchospasm, respiratory arrest,

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hypotension, ventricular fibrillation, and rare cases of Kounis syndrome and stress cardiomyopathy; residual neuromuscular block can occur if not fully reversed [14,15]. Vecuronium exerts minimal direct cardiovascular effects but shares risks of anaphylaxis, bronchospasm, respiratory arrest, and ventricular fibrillation and has been linked to hyperkalemia signals and residual blockade, particularly when reversed with neostigmine alone [13,15]. Pancuronium, due to its vagolytic properties, can cause tachycardia and hypertension through cardiac muscarinic blockade, has been associated with intensive care unit–acquired weakness during prolonged administration, and can result in residual neuromuscular block [13,15].

In patients with neuromuscular disorders, such as myasthenia gravis, the use of NMBAs should be avoided due to increased sensitivity and the potential for prolonged paralysis. Similarly, during procedures involving intraoperative neuromonitoring, the administration of NMBAs is discouraged, as they can suppress electromyographic signals and compromise neuromonitoring accuracy [2,8].

The reversal of deep neuromuscular blockade remains a great challenge. Traditional anticholinesterase agents are often ineffective in reversing profound and rapidly induced blockade, limiting their utility in emergency settings. This limitation contributes to safety concerns surrounding NMBA use [16].

Depolarizing Neuromuscular Relaxants

Although muscle relaxants significantly facilitate tracheal intubation, their use is associated with numerous potential complications [2]. NMBAs, such as succinylcholine, are commonly associated with adverse effects such as hyperkalemia, cardiac dysrhythmia, postoperative myalgia, allergic reaction, prolonged paralysis, raised intracranial pressure, and malignant hyperthermia. In contrast, nondepolarizing muscle relaxants (ND-NMBAs), may result in prolonged neuromuscular blockade, histamine-mediated cardiovascular effects, and rapid reversal challenges in cases of difficult or failed intubation [1].

Findings from the 5th National Audit Project (NAP5) indicated that NMBA use can increase the risk of accidental awareness during general anesthesia [3]. Additionally, most NMBAs have minimal chronotropic effects, although some can cause a slight increase in heart rate following induction [3].

Succinylcholine

Succinylcholine is a rapid-onset, short-acting agent that provides rapid muscle relaxation, allowing full recovery of muscle function within 5 minutes after administration [8]. Owing to its pharmacokinetic properties, it was long considered a primary agent used for endotracheal intubation until alternatives gained popularity in the 1990s [17].

Despite its efficacy, succinylcholine has a significant risk profile, particularly in specific patient populations. Life-threatening metabolic and cardiovascular adverse effects include stroke, renal impairment, and susceptibility to malignant hyperthermia, as well as myalgias, hyperkalemia, masseter muscle spasm, prolonged apnea, and increased IOP and intracranial pressure [3,17]. Rare but serious cases of prolonged paralysis, for over 18 hours, have been documented in patients with undiagnosed pseudocholinesterase deficiency [3].

The mechanism underlying the increase in IOP following succinylcholine administration is not fully understood. It is believed to involve fasciculations of the extraocular muscles and transient choroidal vasodilation. Another proposed mechanism is its cycloplegic effect, which may flatten the lens, enlarge the anterior chamber, and reduce aqueous humour outflow by decreasing tension on the scleral spur [9]. These effects make succinylcholine contraindicated in open-globe injuries or conditions with elevated IOP.

Non-Depolarizing Neuromuscular Blocking Agents

While ND-NMBAs are considered safer alternatives to succinylcholine, they present their own set of limitations. These agents typically have a slower onset of action, prolonged duration, and delayed reversibility, which can pose significant challenges in emergencies requiring rapid airway control [17]. Additionally, the pharmacodynamic response to ND-NMBAs is highly variable between individuals, complicating precise dosing and effect prediction [8].

Rocuronium

Rocuronium is a ND-NMBA with an onset time of approximately 135 seconds. It is primarily metabolized in the liver and excreted in the kidneys. Rocuronium is frequently selected as an ND-NMBA alternative to succinylcholine, especially in rapid sequence induction, owing to its relatively fast onset and favorable intubating conditions. Studies have shown a success rate of 76% in achieving optimal intubation, with acceptable conditions achieved in 64% of cases (n=2192) [3,18,19].

Importantly, the response to neuromuscular blockade differs across muscle groups. Rocuronium acts more rapidly and recovers sooner in the laryngeal muscles than in the adductor pollicis, with the depth of blockade also being less profound in the larynx [19]. This has implications for the timing of intubation and neuromuscular monitoring. Moreover, in elderly

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patients, the onset and duration of action are significantly longer than in younger patients [20].

A continuous infusion of rocuronium at a rate of 9.0 µg/kg/min has been shown to maintain excellent muscle relaxation without significant adverse effects, offering a reliable option for longer surgical procedures [21].

Atracurium

Atracurium is a non-depolarizing neuromuscular blocking agent of the benzylisoquinoline class, commonly used for short- to intermediate-duration muscle relaxation. It has a moderate duration of action and is known to cause histamine release, which can increase the risk of hypotension and allergic reactions [12,13]. FDA Adverse Event Reporting System (FAERS) data indicate that atracurium has the highest reported rates of serious adverse events among the studied NMBAs, including death, hospitalization, and life-threatening complications. Deep neuromuscular blockade induced by atracurium can only be reversed with neostigmine, as sugammadex is not effective [14].

Cisatracurium

Cisatracurium, the stereoisomer of atracurium, is also a benzylisoquinoline NMBA, with higher potency and a lower risk of histamine release than atracurium. It is preferred for continuous infusion, especially in critically ill patients. FAERS analysis shows a relatively lower incidence of adverse events compared with that of other NMBAs, with positive signals in immune and respiratory system disorders, and newly identified hepatobiliary risks. Cisatracurium-induced neuromuscular blockade is reversed using acetylcholinesterase inhibitors, such as neostigmine.

Rocuronium

Rocuronium is a steroidal ND-NMBA with rapid onset and intermediate duration of action, suitable for rapid sequence intubation [12,14]. FAERS data demonstrate the highest number of reported anaphylaxis cases and cardiovascular adverse events among the analyzed NMBAs [14]. Deep neuromuscular blockade induced by rocuronium can be rapidly reversed using sugammadex, offering a significant safety advantage in urgent clinical scenarios [14].

L2 Vecuronium

Vecuronium is a steroidal ND-NMBA with an intermediate duration of action and slower onset than rocuronium. FAERS analysis indicates a lower frequency of serious adverse events relative to other NMBAs [13,15]. Similar to rocuronium, deep blockade with vecuronium can be effectively reversed using sugammadex [13,15].

Sugammadex

This selective relaxant binding agent was designed specifically to reverse the effects of steroidal NMBAs, such as rocuronium and vecuronium. Encapsulating the NMBA molecule, it terminates the neuromuscular blocking activity. However, it is ineffective against benzylisoquinoline compounds, such as atracurium and cisatracurium [8].

Sugammadex is typically administered at the end of surgery to reverse neuromuscular blockade, significantly reducing the incidence of residual postoperative paralysis. Unlike traditional reversal agents, sugammadex can be used at any depth of blockade, even in emergencies, allowing for rapid restoration and spontaneous breathing [8].

The availability of sugammadex has altered the risk-benefit balance of using NMBAs, particularly in emergency intubation scenarios, in which the risk of prolonged paralysis previously limited their use. However, while early evidence is promising, further large-scale studies are needed to confirm its impact on outcomes in emergencies [16].

Technique of Intubation Without Neuromuscular Blockade

In specific surgical procedures, such as spinal and thyroid parotid surgeries, in which intraoperative nerve monitoring is critical, the use of NMBAs is contraindicated. Their avoidance can be necessary in patients with neuromuscular disorders or in critically ill individuals, due to increased risk of adverse effects [3].

In such cases, short-acting opioids with centrally mediated analgesics and antitussive properties are increasingly used to facilitate tracheal intubation. However, successful intubation without NMBAs requires a deeper level of sedation and analgesia, commonly achieved using agents such as propofol, sevoflurane, and sufentanil. This intensified sedation strategy, however, significantly increases the risk of hemodynamic instability, including hypotension and bradycardia, especially in fragile patient populations [2,3]. The goal of these pharmacological substitutes is to reduce the stress response to laryngoscopy and optimize jaw relaxation and vocal cord positioning without inducing neuromuscular blockade [2].

A meta-analysis by Li et al revealed that omitting NMBAs during induction did not significantly worsen jaw relaxation or increase the incidence of coughing. There was a trend toward suboptimal vocal cord positioning, although it was not statistically significant. Nevertheless, hemodynamic instability remains a major concern in these cases, with a high frequency of hypotension and bradycardia observed following

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intubation [2]. One of the viable alternatives to NMBA use is sevoflurane, which demonstrates adequate muscle relaxation during induction and can facilitate endotracheal intubation without additional neuromuscular agents [2].

Authors disagree on how often sedatives used in rapid sequence intubation cause hemodynamic complications. Some studies report hypotension rates with etomidate as high as 30% to 40%, while others report rates as low as 10%. Other data suggest a higher rate of hypotension with ketamine [22]. Contemporary large-scale data from 18 emergency departments (Maia et al, 2025; n=1810) comparing ketamine and etomidate for rapid sequence intubation demonstrated higher 7- and 28-day in-hospital mortality with etomidate (28-day mortality 60.5% vs 54.4%; relative risk, 1.14; 95% CI, 1.03-1.27), whereas new hemodynamic instability within 30 minutes after intubation occurred more frequently with ketamine (24.2% vs 18.9%) [23]. These findings highlight the complex balance between short-term hemodynamic effects and longer-term outcomes, underscoring the importance of patient selection and clinical context when choosing an induction agent.

Intubation Under Deep Anesthesia With Opioids

Opioids are frequently administered during induction to minimize tracheal irritation and ensure favorable conditions in intubation, due to their central analgesic and antitussive properties. They offer a viable alternative to NMBAs, particularly in patients with contraindications to muscle relaxants [3,24]. Opioids suppress sympathetic nervous system activation, thereby blunting the hemodynamic response to laryngoscopy. This makes them especially beneficial in conditions in which cardiovascular stability is critical, such as intracranial hemorrhage, brain tumors, and aortic dissection [24].

However, the optimal opioid dose for rapid sequence intubation remains undefined [24]. A major limitation is the dose-dependent adverse effects of opioids, which include respiratory depression, bradycardia, and hypotension. Rarely, opioid-induced chest wall rigidity should be carefully considered, especially when high doses are used [3]. Examples of commonly used agents include alfentanil, fentanyl, sufentanil, and remifentanil, all of which inhibit sympathetic activation and prevent the subsequent hemodynamic surge [24]. It is important to note that opioids are classified as controlled substances under international narcotic regulations, which can limit their availability or use in certain healthcare settings [25].

Remifentanil

Remifentanil, a short-acting fentanyl derivative, has a rapid onset and offset of action, and is widely considered a promising alternative to NMBAs for tracheal intubation in patients in whom muscle relaxants are contraindicated [3,9]. Remifentanil is metabolized by nonspecific plasma and tissue esterases, making its clearance organ-independent and predictable [3].

Importantly, the dose of remifentanil significantly affects intubation conditions and adverse events and does not result in any notable differences in tracheal intubation success rates, compared with those of NMBAs [3]. Studies have shown that remifentanil can prolong apnea time, compared with succinylcholine, and may result in larger decreases of mean arterial pressure [3,19].

In cases of remifentanil-induced respiratory depression, naloxone can be administered to restore spontaneous ventilation. When lower doses of remifentanil are insufficient to optimize intubation conditions, lidocaine can be added as a supplemental agent. Remifentanil shows promise as an NMBA substitute, but uncertainties remain regarding its hemodynamic safety profile, especially in older adult patients, in whom hypertension and bradycardia are more frequent. Therefore, further studies evaluating different dosing strategies are needed [3,19].

In clinical practice, pharmacological support can be required to counteract remifentanil-related hypotension and bradycardia with phenylephrine, epinephrine, and atropine, often used for stabilization. Administering remifentanil at a dose of 4 μg/kg typically results in satisfactory or optimal intubation conditions for tracheal intubation within approximately 150 seconds [19]. However, a lower incidence of acceptable intubating conditions has been observed when the dose is reduced to 1.5 μg/kg, especially when compared with those of succinylcholine. At a dose of 1.0 μg/kg, remifentanil is associated with the shortest apnea duration, averaging around 3.4 minutes. As the dose increases, the duration of apnea increases as well, reaching its peak at 4.0 μg/kg, when the apnea time can last up to 12.8 minutes, significantly longer than that induced by succinylcholine [3]. Furthermore, larger decreases in mean arterial pressure have been reported following remifentanil administration, compared with those of succinylcholine, highlighting its more pronounced hemodynamic effects [19]. Notably, at a 1.0 μg/kg dose, reminifentanil was also found to be the most effective in attenuating the increase of IOP following tracheal intubation [9].

Remifentanil-Propofol Combination

Remifentanil is frequently administered in combination with propofol to facilitate tracheal intubation without neuromuscular blockade. Through potent suppression of sympathetic responses and airway reflexes, remifentanil reduces the propofol dose required to achieve adequate intubating conditions. This interaction may contribute to improved hemodynamic control

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during laryngoscopy and intubation. The sequence of administration appears clinically relevant. Evidence suggests that administering propofol prior to remifentanil is associated with better intubation conditions and more stable hemodynamic parameters. Nevertheless, both agents exert dose-dependent cardiovascular effects—propofol primarily through vasodilation and myocardial depression, and remifentanil through central sympatholysis and vagotonic action—thereby increasing the risk of hypotension and bradycardia. Careful titration and vigilant monitoring are therefore essential when using this combination, particularly in older adult or hemodynamically unstable patients [2,3].

Alfentanil

Research on the use of alfentanil, a short-acting opioid, in rapid sequence intubation in anesthesia and its effect on muscle stiffness is limited. Both alfentanil and remifentanil are recommended for use in rapid sequence intubation due to their short duration of action. This strong opioid is particularly effective in preventing catecholamine release and the associated hemodynamic response during endotracheal intubation and surgical interventions [24].

Alfentanil has also been shown to significantly reduce the increase in IOP after endotracheal intubation, especially at doses of 20 μg/kg and 40 μg/kg [10].

Due to its respiratory depressant properties and data from cardiopulmonary bypass studies, this drug has been shown to have a lower degree of sequestration in extracorporeal membrane oxygenation systems than fentanyl [26]. Alfentanil is considered less lipophilic and less sequestrating than fentanyl in cardiopulmonary bypass equipment, showing a lower risk of losing the effective dose in the extracorporeal membrane oxygenation circuit [26].

It is characterized by a low extraction rate and limited ability to maintain sedation, which often necessitates the use of adjunct therapies. Importantly, it is the only fentanyl derivative whose non-ionized form dominates at physiological pH, enabling it to rapidly cross the blood-brain barrier and making it a preferred choice for analgesia and sedation [26].

Sufentanil

This drug is commonly used to suppress the hemodynamic responses following endotracheal intubation. Administering lidocaine can help lower the required dose of sufentanil while providing stable hemodynamic control. Research indicates that this drug (as well as propofol) is an effective anesthetic in patients with obesity, whose body composition affects other drug pharmacokinetics. Intravenous lidocaine, at a dose of 1.5 mg/kg, significantly reduces the half maximal effective concentration of sufentanil required for tracheal intubation in individuals with obesity [27].

Fentanyl

Fentanyl, a narcotic, synthetic opioid agonist with a rapid onset and short duration of action and analgesic as well as sedative properties, is widely used to attenuate the hemodynamic response induced by laryngoscopy and intubation [25,28]. Although it is considered less effective in this respect than dexmedetomidine, by suppressing pain stimuli, reducing central sympathetic tone, and activating the parasympathetic system, it can reduce the hemodynamic response without significant adverse effects [25,29]. By fast-acting synthetic μ receptor stimulation, fentanyl reduces the activity of the sympathetic nervous system, increases parasympathetic activity, and affects the central opioid receptors located in the brain regions responsible for controlling speech, pain, emotions, and other functions [28,30].

Based on existing data, the recommended dosage ranges from 1 to 3 μg/kg, with effects typically lasting between 30 and 60 minutes. Administering fentanyl 2 minutes before intubation is advised to achieve optimal hemodynamic stability during the procedure. Precise timing of fentanyl administration is crucial for achieving optimal hemodynamic stability [30].

Intubation Under Deep Anesthesia With Hypnotics

Deep anesthesia with hypnotics during intubation is performed to suppress airway reflexes, reduce stress response, and improve patient comfort. Common hypnotics used include propofol, etomidate, and ketamine. The choice of hypnotics affects rates of hypotension and other complications. These agents offer a rapid onset and enable smooth airway management. Their use and combination depend on the patient's condition and clinical context.

The deep extubation technique reduces emergence agitation and hemodynamic fluctuations compared with awake extubation, particularly in nasal surgeries. However, it requires careful patient selection to avoid hypoventilation or aspiration. It can also significantly reduce the incidence of post-tonsillectomy cough in children with preoperative respiratory diseases [31].

Obstructive sleep apnea, obesity, advanced age, and the presence of invasive devices, such as endotracheal tubes, urinary catheters, nasogastric tubes, and chest tubes, are risk factors for emergence agitation and require additional caution [31]. The deep extubation technique is relevant in operating rooms

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and intensive care units, with tailored protocols for hemodynamic stability and patient safety.

Magnesium Sulfate

Magnesium sulfate, due to its ability to block catecholamine release from adrenergic nerve endings and the adrenal glands, is used to reduce the hemodynamic response during airway obstruction. It also acts as a calcium ion antagonist in vascular smooth muscle, demonstrating antiarrhythmic effects. It causes coronary and systemic vasodilation, leading to a reduction in mean arterial blood pressure [1].

Propofol

Propofol is widely used for its potent hypnotic and sedative properties and its ability to provide rapid, smooth induction with effective suppression of airway reflexes and short recovery time [17]. However, its pharmacodynamic profile is characterized by dose-dependent cardiovascular depression, including reductions in systemic vascular resistance, myocardial contractility, and heart rate, which can lead to hypotension—particularly in patients of advanced age, with hypovolemia, or with hemodynamic compromise [1,2]. Optimal intubating conditions, with minimal hemodynamic adverse effects, are achieved with propofol at a dose of 3 mg/kg, although the 2 mg/kg dose is considered acceptable [17]. The target concentration-controlled infusion system technique allows for precise administration of propofol to achieve and maintain the desired plasma or brain concentrations, ensuring controlled and effective anesthesia management [32]. Propofol's action is primarily based on gamma-aminobutyric acid (GABA) receptors, with additional effects on N-methyl-D-aspartate (NMDA) receptors. Termination of its action occurs primarily through redistribution rather than organ-dependent elimination, making it the preferred agent for patients with organ failure, particularly in intensive care units [33].

One study demonstrated that patients administered magnesium sulfate had better jaw relaxation and less resistance to laryngoscopy blade insertion than those administered propofol. Further analysis also revealed a reduced intubation response, greater vocal cord abduction, and higher intubation condition scores in the magnesium group [1].

Although propofol remains the most commonly used induction agent, it is significantly associated with cardiovascular instability, especially in patients with pre-existing hemodynamic compromise [34]. Total intravenous anesthesia with propofol leads to a greater reduction of heart rate and mean arterial pressure after induction and intubation, compared with sevoflurane, and is also associated with lower IOP [10].

Ketamine

Due to its more stable hemodynamic profile, ketamine, like etomidate, is the preferred agent for intubation in critically ill patients, primarily due to its unique pharmacological properties [34]. Ketamine provides full anesthesia with simultaneous analgesia [33]. Its hemodynamic effects, opposite to those seen in propofol, result from stimulation and inhibition of catecholamine reuptake in the central nervous system.

However, careful clinical assessment remains essential. Although ketamine has historically been considered capable of increasing IOP through cerebral vasodilation and increased perfusion, contemporary systematic reviews demonstrate inconsistent effects on IOP and cerebral perfusion pressure in patients with traumatic or severe acute brain injury. Several studies report stable or even reduced IOP following ketamine administration, while others show no significant change, and only a minority describe transient increases. Importantly, recent meta-analyses have not demonstrated an association between ketamine use and increased mortality or clinically significant worsening of neurological outcomes. Nevertheless, the overall certainty of evidence remains low, and adequately powered randomized clinical trials are still needed to definitively determine its impact on functional outcomes and adverse events [34-37]. Ketamine has the opposite effect of the previously mentioned agents. It elevates blood pressure, heart rate, and cardiac output by stimulating the central sympathetic nervous system, which makes it particularly suitable for trauma patients [22]. Patients receiving ketamine have been observed to require larger volumes of resuscitation fluids over 72 hours than were those given etomidate [22].

Ketamine-Propofol Admixture "Ketofol"

The unique combination of ketamine and propofol, called "ketofol", demonstrates high efficacy in maintaining stable hemodynamic parameters during sedation associated with airway management. It provides opioid-free analgesia, which may reduce the incidence of post-intubation hypotension and reduce mortality and morbidity. Ketofol is a beneficial alternative to opioid sedation. It is being used more frequently due to its stabilizing effect on hemodynamics, while avoiding the adverse effects typically associated with its individual compounds. Ketofol has also been associated with reduced opioid and transfusion requirements, compared with alternative regimens [33].

Sevoflurane

Sevoflurane, a potent inhalation anesthetic with low blood solubility and minimal respiratory irritation, can be an effective alternative to NMBAs, promoting muscle relaxation and

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facilitating intubation [2,32]. Due to its mild odor and low irritating effect, it is the agent of choice for induction in pediatric patients, providing favorable intubation conditions [17]. Additionally, due to the possibility of rapid concentration adjustment and short elimination time, it is widely used in neurosurgery and general anesthesiology [32].

Dexmedetomidine

Dexmedetomidine is an effective and safe adjuvant drug with minimal respiratory depression [35]. Therefore, it is also used as an adjunct during endotracheal intubation [8]. Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that reduces IOP and attenuates the hemodynamic response to laryngoscopy and intubation. It stabilizes the circulatory system, including heart rate, by inhibiting the release of norepinephrine from nerve endings [25,28].

Studies have shown that a dose of 0.5 μg/kg of dexmedetomidine was as effective as fentanyl 2 μg/kg in suppressing the hemodynamic response accompanying intubation [28]. In low doses, it reduces sympathetic activity by reducing norepinephrine release at the neuroeffector junction, which leads to a lower heart rate [28]. Due to its sedative, analgesic, and anxiolytic properties, while not suppressing respiration, this drug helps reduce sympathetic arousal and stabilize hemodynamics during intubation [29].

The combination of dexmedetomidine with opioids is commonly used to reduce cardiovascular reactions accompanying endotracheal intubations [38].

Etomidate

Etomidate is a commonly used induction agent known for its favorable hemodynamic stability. It acts as a positive allosteric modulator of the GABA_A receptor, enhancing inhibitory neurotransmission and producing hypnosis. It has no clinically relevant affinity for alpha-2 adrenergic receptors. However, its use is associated with reversible inhibition of 11β-hydroxylase, leading to suppression of cortisol synthesis for up to approximately 24 hours, particularly after repeated dosing or continuous infusion [33]. This adrenal suppressive effect can lead to organ dysfunction and increased mortality in critically ill patients. For this reason, many anesthesiologists and intensivists avoid using etomidate in critically ill patients [33].

A key advantage of etomidate is its pharmacokinetic profile and ability to maintain cardiovascular stability, allowing anesthesia or deep sedation with minimal hemodynamic disturbances [22]. Because of etomidate's characteristics of rapid sequence intubation and favorable hemodynamic profile in some cases, it is a preferred sedative. Quick action with predictable pharmacokinetics and cardiovascular stability make etomidate a dependable and safe choice in selected patient populations. It also inhibits cytochrome P450 enzymes responsible for corticogenesis, corticosteroid 11β-hydroxylation, and mineralocorticoid precursors, leading to prolonged disruption of cortisol and aldosterone synthesis, critical for patients experiencing major physiological stress [22].

One meta-analysis, including 11 randomized trials with a total of 2704 patients, suggests a strong likelihood that using etomidate as an induction agent for endotracheal intubation is associated with a more than 92% higher risk of mortality (relative risk≈1.9) among critically ill patients, as well as increased risk of adrenal insufficiency. These harmful effects were confirmed through additional analyses. Therefore, when selecting an induction agent in critically ill patients, it is crucial to consider alternative medications [39].

Although etomidate is known for its cardiovascular stability, it should be used carefully since patient reactions can be unpredictable, and it poses a similar risk of hypotension and associated complications as other sedatives known to cause low blood pressure [22].

Alternative Intubation and Ventilation Techniques Without NMBA Use

Given the growing interest in intubation without the use of NMBAs, it is worth exploring alternative techniques that allow for effective airway management and ventilation. One is the non-intubated spontaneous ventilation technique (NIVATS), which revolutionized thoracic surgery by eliminating the need for endotracheal intubation and mechanical ventilation. These techniques combine local anesthesia (infiltration at the incision site and paravertebral, intercostal, vagus, and phrenic nerve blocks) with intravenous sedation and analgesia, often supported by a laryngeal mask airway or oropharyngeal airway [40-42].

NIVATS reduces the risk of lung injury, respiratory depression, CO_2 retention, and atelectasis. It improves ventilation-to-perfusion matching by preserving spontaneous breathing without the need for mechanical ventilation assistance. Additionally, by preventing alveolar overinflation, it minimizes the risk of barotrauma-related injury, alveolar rupture, and overdistension [40-42].

Another solution is the use of video laryngoscopy, which, by improving visualization of anatomical landmarks, increases intubation success rates, particularly in the absence of NMBAs [16].

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Deep inhalation anesthesia can be an alternative to muscle relaxation, although it requires precise monitoring and a high level of expertise.

These methods, including NIVATS, deep inhalational anesthesia, and advanced airway devices, offer valuable options for airway management optimization when muscle relaxants are contraindicated or associated with increased risk. Their safe application requires careful patient selection, clinical expertise, and continuous monitoring of efficacy and safety.

Comparison of the NMBA Group With the Non-NMBA Group

NMBAs are commonly used during endotracheal intubation to facilitate muscle relaxation and improve intubation conditions. Their necessity and benefits compared with intubation without NMBAs have been the subject of ongoing research.

A meta-analysis examining postoperative outcomes found no significant difference in the incidence of postoperative sore throat or hoarseness, the most commonly observed postoperative complications related to intubation discomfort, at any time point between patients who received NMBAs and those who did not [2].

When assessing intubation conditions, data from 6 trials involving 917 patients showed that NMBA use was associated with a higher overall rate of acceptable intubation conditions. However, in 5 other trials including 843 patients, no significant difference between groups was found. Similarly, jaw relaxation measured during the endotracheal intubation (n=495) showed no significant differences, and no major advantage was observed in terms of reducing coughing, improving vocal cord position, or decreasing the need for hemodynamic intervention during intubation. The requirement for pharmacological intervention due to coughing was also comparable [2].

Notably, when comparing first-attempt success rates for endotracheal intubation, patients who received NMBAs had a higher success rate (85%) than did those who underwent intubation with sedation alone (72%) [16]. This indicates that NMBA use is associated with improved first-attempt success rates.

The meta-analysis by Li et al, which included 1176 patients, reinforced these findings by showing that NMBA induction led to a higher overall incidence of acceptable intubating conditions. Furthermore, 6 trials involving 924 participants reported a significantly higher occurrence of poor intubation conditions in patients who did not receive NMBAs [2]. Despite the improved muscle relaxation with NMBA use, omitting NMBAs does not appear to increase the risk of postoperative pharyngeal discomfort [2].

It is possible that the full muscle relaxation achieved with NMBA administration leads anesthesiologists to assign higher intubation scores (ie, “excellent” or “good”), whereas the group without NMBAs is more frequently rated as “poor”. Interestingly, this rating difference occurs despite the lack of observed negative impact on jaw relaxation, vocal cord positioning, or the incidence of coughing during intubation [2].

In terms of alternatives, no significant difference in first-attempt tracheal intubation success has been found between the use of remifentanil and NMBAs [3]. It is important to consider that physiological changes related to aging can prolong drug activity, potentially impairing intubation conditions or increasing the risk of failed intubation [20].

Conclusions

A summary of the key characteristics of each drug is presented in **Table 1**. In conclusion, performing endotracheal intubation without NMBAs does not increase postoperative risks, although it might result in poorer intubation conditions. While tracheal intubation is a routine component of modern airway management, it remains a high-stakes intervention, especially in critically ill patients. The choice and timing of pharmacological agents used during intubation have a profound impact on patient outcomes, influencing factors such as hemodynamic stability, IOP, intracranial pressure, oxygenation, and the risk of complications, including aspiration or prolonged apnea.

NMBAs, although not always necessary, are often crucial in optimizing intubation conditions by facilitating muscular relaxation, improving vocal cord visualization, and reducing airway trauma. In the context of neuronal monitoring, particularly in procedures requiring electromyography endotracheal tube replacement, the use of NMBAs must be judicious, as excessive blockade can obscure important intraoperative signals. Therefore, the selection of agents must strike a balance between efficacy, duration of action, and potential interference with surgical goals.

However, growing evidence supports the feasibility and safety of intubation without NMBAs, particularly in patients with contraindications to NMBAs or when neuromonitoring is essential. The use of short-acting opioids (remifentanil and alfentanil), hypnotics (propofol, ketamine, and etomidate), and adjunct agents (magnesium sulfate and dexmedetomidine) offers an effective pharmacological strategy to suppress airway reflexes, blunt the hemodynamic response, and facilitate safe intubation. These agents allow clinicians to tailor anesthesia to individual patient profiles, preserving respiratory drive, minimizing cardiovascular instability, and avoiding neuromuscular complications.

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Table 1. Summary of key features of the individual drugs.

Drug	Mechanism of action	Advantages	Limitations and adverse effects	Clinical notes
Propofol	– It represents 2,6-diisopropylphenol [43] – Used only intravenously, because of bitter taste and low oral bioavailability [43] – Standard induction doses are 2-2.5 mg/kg [33] – Acts by activating the central inhibitory neurotransmitter gaba to produce hypnosis [43] – Mainly metabolized in the liver but can also be exhaled [43]	– Insoluble in water [43] – It provides effective and safe anesthesia in mg patients [32] – Rapid onset, short duration of action, and suppressed airway reflexes [32] – Lipoid emulsion of propofol possesses antioxidant properties [43]	– Not suited for enteral or other routes of administration [43] – Crosses the blood–brain barrier (bbb) quickly and causes unconsciousness [43]	– It is more potent during shock, meaning lower doses are more effective [33] – Strong vasodilating properties, along with its tendency to suppress heart function [33] – Cardiorespiratory depressor effect [33] – Called “milk of anesthesia” [43] – Very solid antiemetic effect [43]
Etomidate	– Hypnotic agent, positive allosteric modulator on the γ-aminobutyric acid type A receptor [44] – Rapidly metabolized in the liver by hepatic esterases through hydrolyzation (into an inactive carboxylic acid) [44]	– Remarkably stable cardiorespiratory profile [44] – Favorable hemodynamic and respiratory properties [44]	– Unsuitable for administration by a prolonged infusion (suppresses the adrenocortical axis by the inhibition of the enzyme 11β-hydroxylase) [44] – Well known for its adrenal toxicity (suppression of the adrenocortical axis) [44]	– Unclear origin of involuntary muscle movements occurrence [44] – Unsuitable for administration to critically ill patients (increase in mortality) [44] – Volumes of distribution related to high solubility in fat [44]
Ketamine	– Classified as a narcotic product [46] – N-methyl-D-aspartate (NMDA) receptor antagonistic [45] – Dissociative effect, inhibition of descending inhibitory systems and astrocytic pronociceptive systems [45] – The standard dose is 1-2 mg/kg [33]	– Smaller risk of hypotension or a respiratory depressant effect [45] but still possible in severely injured patients [46]	– Uncontrollable “psychotic” adverse drug reactions, street drug (“angel dust”) [45]	– Cardiorespiratory stimulant effect [33] – Relatively short duration of action [45] – Excreted mainly by the kidneys [45] – Local anesthetic effect and anti-inflammatory properties [45]

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Table 1 continued. Summary of key features of the individual drugs.

Drug	Mechanism of action	Advantages	Limitations and adverse effects	Clinical notes
Remifentanil	– Mu-opioid receptor agonist in central nervous system to induce sedation and analgesia [47] – Excellent tracheal intubation conditions achievable up to plateau at 4 μg/kg [48] (with 39% vs 28% in patients above 80 years old [19])	– Rapid onset and offset, short duration of action, and experiences minimum tissue accumulation [47] – High lipophilicity, fast distribution, and metabolism by plasma esterase enzymes [47]	– Significant toxicology exertion concerning dose-related respiratory depression (respiratory rate reduction, tidal volume, and minute ventilation) [47] – Chest-wall rigidity, nausea, and vomiting [47] – Risk factors include: age, coexisting medical illness, genetics [47]	– 42% vs 25% on first-attempt success rate [19] – Rapid onset effects, reduction of apnea duration [48] – Arterial hypotension increases with the dose increase [48]
Fentanyl [49]	– Highly potent synthetic mu-opioid receptor agonist – Many routes of administration – Primarily as metabolites in the urine elimination	– Highly lipophilic, which results in rapid absorption by highly perfused tissues – Efficacious analgesic profile – Instantaneous absorption and onset	– Not recommended for oral administration – Long terminal elimination driven by lipophilicity distribution into muscle and adipose tissue	– Primarily metabolism and urinary excretion of metabolites elimination – "Fentanyl rebound" phenomenon effect during secondary plasma peaks in post-surgical recovery – Long terminal elimination
Alfentanil	– Decrease in total plasma concentration and the increase in unbound plasma concentration [50] – Particularly effective in preventing catecholamine release [24]	– A short-acting opioid [24] – Recommended for use in rapid sequence intubation [24] – It significantly reduces the increase in intraocular pressure [18] – It crosses the blood-brain barrier, making it a preferred choice for analgesia and sedation [26]	– A need for higher doses of alfentanil for sedation in extracorporeal membrane oxygenation [26]	– Respiratory depressant properties [26] – Low extraction rate and limited ability to maintain sedation [26]
Sufentanil	– Shows cardiopulmonary bypass induced fluctuations in plasma concentration [50]	– Suppress the hemodynamic responses following endotracheal intubation [27] – Effective anesthetic in patients with obesity [27]	– Observed delayed awakening [50]	– A supplementary bolus before cardiopulmonary bypass initiation should be administered prior to initiating cardiopulmonary bypass, after which the dose should be decreased to prevent prolonged sedation [50]

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Table 1 continued. Summary of key features of the individual drugs.

Drug	Mechanism of action	Advantages	Limitations and adverse effects	Clinical notes
Dexmedetomidine	– Selective alpha-2 adrenergic receptor agonist [28] – Inhibits the release of norepinephrine from nerve endings [28] – It reduces sympathetic activity by reducing norepinephrine release at the neuroeffector junction [28]	– Does not depress respiration [25] – That reduces intraocular pressure and limits hemodynamic response to laryngoscopy and intubation [25] – Helps reduce sympathetic arousal and stabilize hemodynamics during intubation [29]	– There are no hemodynamic adverse effects [28]	– Used as an adjunct during endotracheal intubation [8] – Stabilizes the circulatory [25] – Provides anxiety relief while minimally affecting spontaneous breathing [33]
Ketofol [33]	– Unique combination of ketamine and propofol	– It provides opioid-free analgesia – Demonstrates high efficacy in maintaining stable hemodynamic parameters during sedation – Stabilizing effect on hemodynamics	– It causes hemodynamic disturbances, but they are fewer than either of the original compounds	– Cardiorespiratory balanced effect – A beneficial alternative to opioid sedation – It is associated with reduced opioid and transfusion requirements
Sevofluarane	– A potent inhalation anesthetic [32] – Rapid concentration adjustment and short elimination time [32]	– It is characterized by low blood solubility and minimal respiratory irritation [32] – Mild odor, and low irritating effect [17]	– Partial loss of flow-metabolism coupling due to direct intrinsic cerebral vasodilatory [50]	– It provides effective and safe anesthesia in MG patients and achieves higher levels of muscular relaxation than with propofol [32] – High concentrations' avoidance [50] – An effective alternative to NMBAs [2]
Magnesium sulfate [1]	– Ability to block catecholamine release from both adrenergic nerve endings and the adrenal glands – Calcium ion antagonist in vascular smooth muscle	– It causes coronary and systemic vasodilation	– Observed tendency to vocal cords abduction	– Antiarrhythmic effects

Nevertheless, the choice of agents requires a nuanced understanding of their pharmacodynamic properties, potential adverse effects, and interaction with the clinical condition of the patient. New approaches and discoveries, such as the ketamine and propofol combination ketofol, demonstrate promising methods in the combination of sedation with hemodynamic preservation.

In conclusion, while intubation without NMBAs may not yet be standardized, it represents a valuable option in modern airway management. Individualized drug selection, based on the patient's physiological state, the surgical context, and each drug's pharmacologic profile, is the key to minimizing peri-intubation complications. Further research is needed to refine protocols and define patient groups that may benefit the most. Ongoing clinical awareness will be essential to ensuring safe, effective airway management across diverse patient populations.

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