

INTRODUCTION

Airway management is a fundamental aspect of anaesthetic practice and of emergency and critical care medicine. Endotracheal intubation (ETI) is a rapid, simple, safe and non surgical technique that achieves all the goals of airway management, namely, maintains airway patency, protects the lungs from aspiration and permits leak free ventilation during mechanical ventilation, and remains the gold standard procedure for airway management.

Indication for endotracheal intubation: ⁽¹⁾

1. The need to deliver positive pressure ventilation.
2. Protection of the respiratory tract from aspiration of gastric content.
3. Surgical procedures involving head and neck.
4. Non supine positions that preclude manual airway support.
5. Surgical procedures involving cranium, thorax, or abdomen.
6. Non operative indications
 - Profound disturbance in consciousness with the inability to protect the airway.
 - Tracheobronchial toilet.
 - Sever pulmonary or multisystem injury associated with respiratory failure.

A marked stress response including hypertension, tachycardia, arrhythmias ⁽²⁾ and an increase in intracranial pressure⁽³⁾ often follows direct laryngoscopy ⁽⁴⁾. Although these alterations are short lived, they might result in adverse cardiovascular events ⁽⁵⁾ in patients with⁽⁶⁾ or even without⁽⁷⁾ underlying cardiovascular disease. This response can be harmful specially in former group. It has been suggested that laryngoscopic stimulation of oropharyngolaryngeal structures and distension of the supraglottic tissues may have important role in this hemodynamic stress response^(8,9).

Nerve supply of the airway:

The upper airway extends from nares and mouth to the glottis. Cricoid cartilage is the boundary between the upper and lower respiratory tract.

Oral cavity is supplied by the branches of trigeminal, facial, glossopharyngeal and hypoglossal nerve. Nasal cavity is supplied by anterior and posterior ethmoidal nerves. It is also supplied by anterior-superior alveolar branch and infra orbital branch of maxillary nerve.

Base of the tongue, upper part of epiglottis and pharyngeal walls are supplied by glossopharyngeal nerve. Lower part of the epiglottis and supra glottic parts of the pharynx are supplied by superior laryngeal branch of vagus nerve⁽¹⁰⁾.

The mucous membrane of the larynx receives its nerve supply from both the superior and recurrent laryngeal nerves. The superior laryngeal nerve arises from inferior ganglion of vagus but receives a small branch from the superior sympathetic ganglion. At the level of greater horn of hyoid it divides into an internal and external branch. The internal branch is purely sensory. The upper branch supplies the mucous membrane of the lower part of the pharynx, epiglottis, vallecula and vestibule of the larynx.

The lower branch supplies the aryepiglottic fold and mucous membrane of the posterior part of rima glottidis. The lower part of the larynx below the vocal cords is supplied by the recurrent laryngeal nerve. The external branch of superior laryngeal nerve supplies the cricothyroid muscle and all the rest of the muscles of larynx are supplied by recurrent laryngeal nerve⁽¹⁰⁾.

Physiology of the airway reflexes:

Lower pharynx, epiglottis and larynx contain numerous sensory receptors which respond to chemical, thermal and mechanical stimuli. The mechanoreceptors are abundant especially in the lower pharyngeal wall, epiglottis and vocal cords. Stimulation of these mechanoreceptors can produce reflex motor responses like cough, hiccup and also reflex sympathetic stimulation and cardiovascular pressor response⁽¹¹⁾.

The sensory unit consists of free nerve endings that lie between the mucosal cells of the airway epithelium. Sensory units appear to be particularly abundant over the arytenoids cartilages and are also found on the laryngeal side of the epiglottis. The superior laryngeal nerve carries a large proportion of small diameter myelinated fibres (group III, A - delta, B sensory fibres) which carry afferent impulses. The recurrent laryngeal nerve also carries sensory fibres mainly from rapidly adapting receptors that are activated by light touch. These receptors are abundant on the inferior surface of the vocal cords.^(4, 7)

Afferent fibres in the laryngeal nerves project centrally to the nucleus tractus solitarius particularly caudal and posterior parts. The central reflex site is in medulla. The nucleus tractus solitarius at which the afferent impulses terminate is closely linked with vasomotor centre. Sympathetic activity originates within the reticular formation of the lower third of pons and the upper medulla from regions that are represented bilaterally.

Together these areas are referred as the vasomotor centre. The neurons of vasomotor centre are under constant influence of afferent impulses that originate from mechanoreceptors located within the heart, lungs and arteries^(11,12).

Each efferent sympathetic pathway is composed of a pre-ganglionic neuron. The cell bodies of pre-ganglionic neurons lie within the thoracic and upper lumbar spinal cord. These fibres pass from the cord via anterior routes of each spinal nerve and then via the white ramus to synapse with post ganglionic cell bodies located within the ganglia of the sympathetic chains.

From these ganglia post ganglionic sympathetic nerves pass to their effector organs. Pre ganglionic fibres of T8 to T12 synapse in the adrenal medulla. Stimulation of these causes release of catecholamines from the adrenal medulla into the circulation⁽¹²⁾.

Suggested mechanism of haemodynamic response:

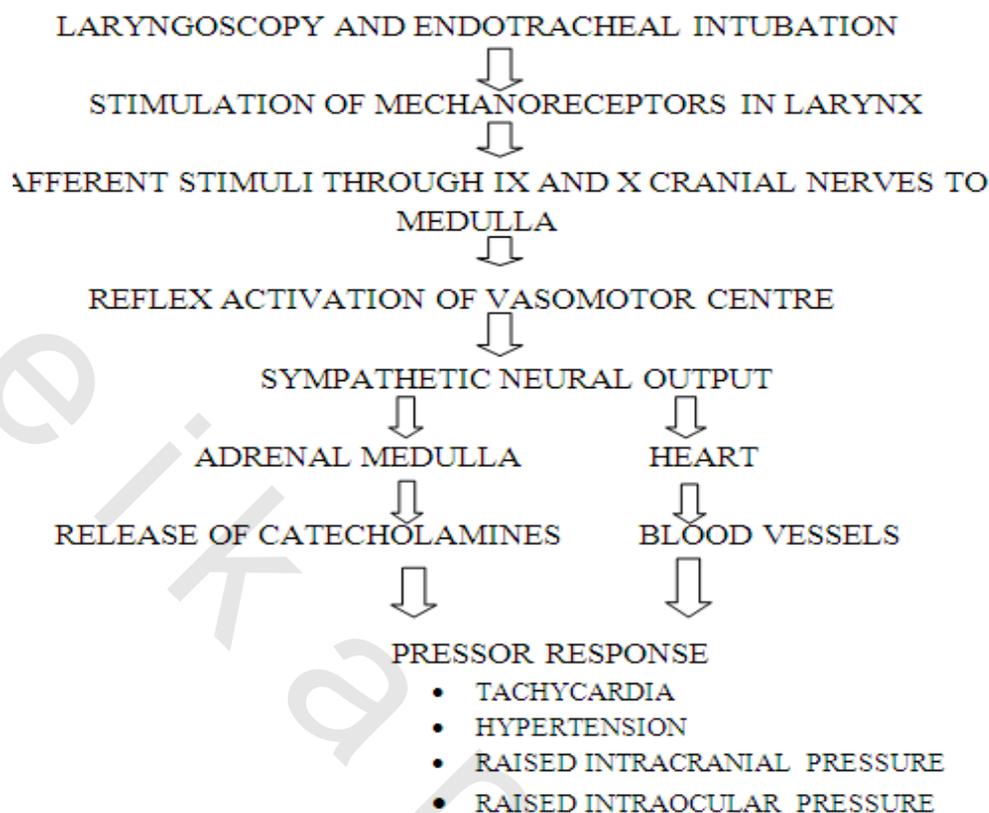


Figure (1): Mechanism of haemodynamic response

Methods to decrease stress of intubation:

I- Non pharmacological methods

- Limiting time of laryngoscopy and intubation.
- Leave the patient upright till the last possible time and intubate in 20 degree head up.
- Non-touch intubation(vedio assisted laryngoscopy).
- Applying topical local anaesthetics or airway nerve blocks (glossopharyngeal n,superior laryngeal nerve or transtracheal injection) during fiberoptic intubation.

II- Pharmacological methods

A large array of pharmacological agents are used to attenuate the hemodynamic responses to the laryngoscopy and tracheal intubation such as:

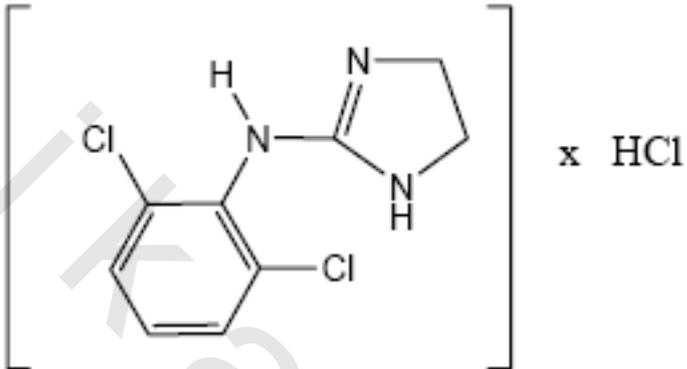
- Increasing depth of anaesthesia,
- Large doses of narcotics such as fentanyl 6 µg/kg,
- Injection of lidocaine IV before intubation
- Drugs acting on cardiovascular system to reduce heart rate or blood pressure such as
 - Esmolol 1.5-2 mg / kg 3 minutes before intubation
 - Nicardipine 20 mcg/kg before intubation.

Clonidine

Pharmacokinetics

Clonidine is classified as an imidazoline. It is the prototypical alpha-2 receptor agonist. Its primary effect is at central pre- and postsynaptic alpha-2 receptors. It has an alpha-2 to alpha-1 selectivity ratio of 200:1. Clonidine has a half-life of 12-16 hours, and it is available for oral⁽¹³⁾, transdermal⁽¹⁴⁾, epidural⁽¹⁵⁾, and intravenous⁽¹⁶⁾ administration.

Table (1): Chemical structure of clonidine.⁽¹⁶⁾

Clonidine	
 <p style="text-align: center;">Chemical structure of clonidine</p>	
Systematic name	<i>N</i> -(2,6-dichlorophenyl)-4,5-dihydro-1 <i>H</i> -imidazol-2-amine
Clinical data	
Trade names	Catapres, Kapvay, Nexiclon
Pregnancy cat.	B3
Legal status	Prescription only
Routes	Oral, epidural, IV, transdermal, topical
Pharmacokinetic data	
Metabolism	Hepatic
Half-life	12-16 hours
Excretion	Urine
Chemical data	
Formula	C ₉ H ₉ Cl ₂ N ₃
Molecular mass	230.093 g/mol

Pharmacodynamics

Effects on the cardiovascular system ⁽¹⁷⁾

The pharmacodynamic profile of alpha-2-adrenoceptor agonists in the cardiovascular system is complex. Alpha-2-adrenoceptor agonists can produce hypotension or hypertension at different doses. Lower doses of these agents result in sympatholysis mediated by the CNS alpha-2 adrenoceptor subtype. Alpha-2-adrenoceptor agonists appear to attenuate the CNS “set-point” at which blood pressure is regulated. The sustained decrease in blood pressure and heart rate are thought to be due to increased parasympathetic (vagal) activity, a centrally-mediated inhibition of the locus ceruleus adrenoceptors, or decreased norepinephrine release at the neuroeffector junction. Imidazoline receptors in the brainstem may also be involved in increasing vagal tone.

The site for the sedative action of alpha-2 agonists is the locus ceruleus of the brainstem, whereas the principal site for analgesic action is probably in the spinal cord. In the heart, the dominant action of alpha-2 agonists is to decrease heart rate by increasing vagal tone and inhibiting the cardio-accelerator nerve. In the peripheral vasculature, both presynaptically mediated vasodilatation and postsynaptically mediated vasoconstriction occur.

Sedation and analgesia

Alpha-2-agonists produce their sedative–hypnotic effect by an action on alpha-2 receptors in the locus ceruleus and produce their analgesic effect by an action on alpha-2 receptors within the locus ceruleus and the spinal cord. However, there is clear evidence for both peripheral and supraspinal sites of action. This results in sedation, hypnosis, anxiolysis, and analgesia. Sedation associated alpha-2-agonists is different from that experienced with GABAminergic agents: the sedative effects of clonidine appear to act through the endogenous sleep-promoting pathways.⁽¹⁸⁾

Table (2): Alpha-2-adrenoceptor mediated physiologic responses at various tissues.⁽¹⁹⁾

Alpha-2-adrenoceptor mediated physiologic responses at various tissues	
Tissue	Response
Nervous system brain, spinal cord and eye	Hypotension, bradycardia, sedation–hypnosis, analgesia, mydriasis and decreased intraocular pressure
Vascular smooth muscle	Contraction
Respiratory system	Decreased minute ventilation (minimal), no effect on hypercapnic and hypoxic drive
Gastrointestinal tract	Decreased salivary and gastric secretions, increased large bowel absorption
Renal	Increased diuresis and glomerular filtration, decreased renin release
Endocrine Pancreatic-beta cells Hypothalamus-pituitary axis	Decreased insulin release Increased growth hormone release, decreased adrenocorticotrophic hormone, cortisol, and vasopressin release
Adipose tissue	Inhibition of lipolysis

Effects on the other systems

Several other organ systems have pharmacodynamic responses mediated by alpha-2-adrenoceptors. Alpha-2-adrenoceptor agonists cause minimal minute ventilation depression and have no effect on hypercapnic and hypoxic ventilatory drive in healthy human volunteers. In the kidney, alpha-2-adrenoceptor activation promotes diuresis, decreases the secretion of vasopressin and renin, and increases the release of atrial natriuretic factor. Prejunctional alpha-2-adrenoceptor agonists have been shown to decrease gastric and salivary secretions. Clinically insignificant inhibition of insulin release by alpha-2-adrenoceptor activation has been demonstrated. Other endocrine effects include increased growth hormone release and inhibition of adrenocorticotrophic hormone, cortisol, and adipose tissue lipolysis.⁽²⁰⁾

Clonidine in perioperative medicine⁽²¹⁾

Alpha-2-adrenoceptor agonists have anaesthetic-sparing, analgesic, and sympatholytic effects. Modulation of the adrenergic response to surgical stress may reduce patient morbidity and mortality. No pharmacologically significant adverse effects have been discovered for alpha-2-adrenoceptor agonists, other than an extension of their known physiological effects: hypotension and bradycardia.

In recent years, there has been enormous interest in the perioperative use of beta-adrenergic receptor blockers and their effectiveness in reducing perioperative risk. These agents are competitive antagonists of catecholamine activity at adrenergic nerve terminals. Used prophylactically, beta-blockers are effective at achieving their primary goal: heart rate control. However, once the stress response is activated, effective rate control may be impossible. Therefore, agents that reduce catecholamine secretion may be useful adjuncts. Alpha-2 adrenergic agonists such as clonidine have the ability to maintain an optimal myocardial oxygen supply-to-demand ratio results from decreasing oxygen demand (perioperative hyperdynamic responses), while maintaining myocardial perfusion. Although hemodynamic stability may be clinically important in certain high-risk patients, systemic side effects resulting from alpha-2-adrenoceptor agonist therapy may reduce any benefit. Excessive sympatholysis may be detrimental in patients requiring central sympathetic tone for adequate perfusion pressures, such as in hypovolemia, hemorrhage, sepsis, and heart failure.

Alpha-2-adrenoceptor agonists have significant sparing effects on intravenous and inhalational anaesthesia, and hence sedation. The mechanism of sedation and opioid-sparing effects of alpha-2 adrenoceptor agonists may be the result of either pharmacodynamic or pharmacokinetic mechanisms.

Clonidine has well-established analgesic properties. It has been administered by a variety of routes for perioperative pain control, alone or in combination with local anaesthetics or opioids.

The precise mechanisms of the analgesic properties of clonidine have not been fully elucidated. Stimulation of the locus ceruleus may activate the descending medullospinal noradrenergic antinociceptive pathway, resulting in the suppression of spinal neurotransmission. In the substantia gelatinosa of the dorsal horn, alpha-2-adrenoceptors may independently inhibit the nociceptive neurotransmission of peripheral A delta and C fibers.⁽²²⁾

However, ligand-binding studies have demonstrated an interdependence of opioid and alpha-2-adrenergic receptors in the modulation of peripheral C fiber transmission. Other possible mechanisms of alpha-2-adrenoceptor antinociception include inhibition of the release of substance P by primary afferent neurons in the dorsal horn, suppression of wide dynamic range neurons, stimulation of acetylcholine release in the dorsal horn, and activation of the serotonergic systems that mediate analgesia.⁽²²⁾

It also benefits in postoperative pain management, especially when administered epidurally or intrathecally. Moreover, clonidine provided better pain management when combined with opioids, with or without local anaesthetics, and is stable and compatible with these drugs.⁽²³⁾

In recent years, clonidine which is a selective partial agonist for α -2 adrenoceptor has been used to prolong spinal Anaesthesia. It is known to increase both sensory and motor block of local anaesthetics. It also modulates input at dorsal horn by increasing potassium conductance. Clonidine also has cholinergic effects and increases the amount of acetylcholine available for modulating analgesia. The analgesic effect following its intrathecal administration is mediated through activation of post synaptic α -2 receptor in substantia gelatinosa of spinal cord.⁽²⁴⁾

Pregabalin

The gabapentinoids; gabapentin and its developmental successor pregabalin are structural derivatives of the inhibitory neurotransmitter GABA although they do not bind to GABA_A, GABA_B or benzodiazepine receptors, nor do they metabolically convert into GABA, or alter its uptake or degradation.⁽²⁵⁻²⁷⁾

They were originally developed as spasmolytic agents.^(28,29) Their anticonvulsant, anxiolytic and sleep-modulating utility permitted their use as adjuncts for management of generalized or partial epileptic seizures resistant to conventional therapies.^(29,30) Their therapeutic armamentarium was furthermore expanded over time to control chronic pain conditions [*diabetic neuropathy, post herpetic neuralgia, central neuropathic pain, and fibromyalgia*] as well as some acute pain conditions [*inflammatory or insional injuries (especially laparoscopic and daycare surgeries)*].⁽³¹⁻³³⁾

Pregabalin pharmacology

Pharmacokinetically; Unlike its predecessor gabapantin, pregabalin absorption is non-saturable, resulting in an advantage of having **linear pharmacokinetic profile**.^(29,34)

It **absorbs** rapidly when administered on an empty stomach, with average **bio-availability** exceeding 90%, reaching peak plasma concentrations within one hour. This absorption decreases when given with food permitting a decrease in C_{max} by approximately 25 to 30% and a delay in T_{max} to approximately 2.5 hours.^(29,34,35)

The drug **distributes** non bound to plasma proteins, crosses blood brain and placental barriers and is found in milk. Its volume of distribution in humans after an oral dose is approximately 0.56 L/kg.^(27,29,34,36)

Drug **metabolism** is negligible, i.e. sparsely metabolizes into N-methyl pregabalin.

Introduction

It is approximately 98% is excreted unchanged in urine signifying that drug **excretion** is primarily renal with an elimination that is nearly proportional to creatinine clearance. Thus a 50% reduction in pregabalin daily dose is recommended in patients with creatinine clearance between 30 and 60 mL/min.^(27,34-38)

The $t_{1/2}$ range from 5-6.5 hrs, with the merit of being of longer duration of action than gabapantin, so requires less frequent daily dosing.^(33-35,38)

Pharmacodynamically; Pregabalin, act by binding selectively to the $\alpha 2$ - δ subunit of presynaptic, voltage-gated calcium channels (widely distributed throughout the central and peripheral nervous system).^(27,34, 39-42) This subunit is mainly extracellular with a single transmembrane domain and five intracellular carboxyl terminal amino acids. It consists of two disulfide-linked peptides ($\alpha 2$ and δ) that are encoded by the same gene.^(43, 44) It is highly glycosylated, and when expressed with other Ca channel subunits, it is likely involved in VGCC assembly, stabilization and cellular trafficking. It also increases and stabilizes current amplitude, channel binding sites and binding affinity for N-type VGCC ligands.⁽⁴³⁻⁴⁵⁾

Pregabalin binding to such subunit, will transiently inhibit Ca influx, thereby reducing release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, substance P and CGRP.^(29,34,46,47) This inhibitory modulation of neuronal excitability, occurs particularly in areas dense in synaptic connections such as the neocortex, amygdala, and hippocampus. In contrast, pregabalin it does not bind to other types of Ca channels, especially those controlling cardiovascular functions.^(27,29,48, 49)

The binding of pregabalin to the $\alpha 2$ - δ subunit was found to be 6 times more potent than that of gabapantin which reasons why it is 3–10 times more potent antiepileptic and 2–4 times more potent analgesic than gabapantin.^(34,50) This simply means that it provides equivalent efficacy at much lower doses, with the promise of less dose-related adverse effects.⁽⁵¹⁾

Adverse drug reactions are mild-to-moderate, mostly dose dependent, usually transient especially on short term use. In clinical trials, the most frequently reported were dizziness in 29% and somnolence in 22%.⁽⁵²⁾ Dry mouth, blurred vision, peripheral edema, vertigo, irritability and weight gain, ...etc are less commonly retrieved (<10%) while case reports of myoclonus, atetosis, gynecomastia, depression, suicidal thoughts, ...etc. are infrequent or rare.^(27,34,53-55) Withdrawal manifestations as seizures, restlessness, insomnia, and anxiety appear upon abrupt discontinuation after long-term use, which calls for the need of gradual withdrawal over a week. Overdosing frequently occurs in patients with impending renal failure, so therapeutic drug monitoring may be needed to monitor therapy or confirm toxicity. If so is the case, a 4-hs hemodialysis treatment, will reduce plasma pregabalin concentrations to approximately 50 %.

Pregabalin is **contraindicated** in patients with known hypersensitivity to any of its components.⁽²⁷⁾

No kinetic **drug-drug interactions** have been identified,^(27, 56) yet minimal potential dynamic interactions may occur if given with CNS depressants as opioids (*pregabalin is synergistic with opioids in lower doses*), benzodiazepines, barbiturates, ethanol.^(27, 57)

AIM OF THE WORK

To compare the effect of premedication with a single oral dose of pregabalin (150 mg) versus oral clonidine (0.2mg) on haemodynamic response to tracheal intubation and the level of preoperative sedation.

PATIENTS

After approval of Ethical Committee of Faculty of Medicine and having written informed consent from patients, a double blinded study was carried out in Alexandria Main University Hospitals on 40 patients 20 for each group. The patients belonged to ASA physical status classification I or II, of both sex, 18-45 years old and scheduled for elective superficial surgery (neck [lipoma, excisional LN biopsy], breast mass, plastic surgery in lip and face) under general anaesthesia with endotracheal intubation.

Exclusion criteria:

1. History of cardiac disease or asthma.
2. Impaired kidney or liver functions.
3. History of drug or alcohol abuse.
4. Anticipated difficult intubation.
5. Morbid obesity.
6. History of taking antihypertensive and antidepressants drugs

Patients were randomly categorized using closed envelop technique into two equal groups (twenty patients each):

Group I: Patients received 150 mg of pregabalin orally 90 minute before operation.

Group II: Patients received 0.2 mg of clonidine orally 90 minute before operation.