# INTRODUCTION

Postoperative laryngeal complications that may occur during emergence from general anaesthesia with tracheal extubation represent common and distressing events to both patients and anaesthetists, and it may lead to series of serious life threatening situations, respiratory complications occurring after extubation are three times more common than complications occurring during general anaesthesia induction and endotracheal intubation.(1)

Most of these laryngeal complications occur due to a known mechanism involving trauma to mucosa due to airway instrumentation and intubation, mucosal ischaemia following decreases in the blood supply and the venous return related to high pressures of the airway device's cuff, the erosion and dehydration of delicate mucosal tissues, and the resulting inflammation.(2)

Vocal cords ulceration and granulation tissue lesions were seen more frequently in the inter-arytenoid and subglottic area when the standard polyvinyl chloride (PVC) tube was used. This was presumably due to the elastic recoil of the standard PVC tube, which exerts more pressure against the posterior wall of the larynx.(3)

Contact ulcer granuloma is the most common late complication of tracheal intubation and should be suspected if the patient complains of prolonged hoarseness which may last up to 99 days, the site of the granuloma was usually at the tip of the vocal processes of the arytenoid cartilages, due to, among other things, their incessant movement.(4)

Laryngoscopy and moving an airway device may produce excitation of sensory C fibres and it is associated cough, postoperative sore throat and bronchoconstriction. Commonly these changes are spontaneously reversible.(2)

## Risk factors:

There are many risk factors for postextubation laryngeal complications including factors related to the patient, the operation, and the endotracheal intubation technique itself.

Factors related to the patient including age, sex, medical history of smoking, respiratory system affection primarily or secondary as due to morbid obesity, severe gastroeosophogeal reflux or any unexpected allergic responses.

Female gender and old age are two risk factors this has been hypothesized to be due to having a more friable glottic mucosa so it is more vulnerable to trauma and injury, a relatively larger endotracheal tube to trachea ratio may also be a contributor.(5,6) Systemic diseases also have its effect e.g. Systemic atherosclerotic changes may affect the micro-circulation of the larynx leading to making it more vulnerable to the harmful effect of the endotracheal tube cuff pressure.(7)

Factors related to the operation including positioning if the head and neck is in lower position than the heart e.g. Trendlenburg, also patients who were placed in prone position (as in posterior fossa neurosurgeries), or in lithotomic position reported a higher rate of post-operative laryngeal complications than those who were supine during surgery this

may be contributed to venous congestion. Head and neck surgeries sequels e.g. recurrent laryngeal or superior laryngeal nerve injuries (which are common in thyroidectomy operations especially for malignant thyroids), haematoma, oedema and distortion of the upper airway anatomy as in deep neck abscesses drainage.[8]

Finally, the technical factors related to conditions and techniques to reach and keep endotracheal intubation as duration of laryngoscopy, number of intubation trials, both pharyngeal and oesophageal perforation have been reported following repeated attempts at intubation using a rigid stylet. Although in both cases it was not known whether the tip of the stylet protruded beyond the lumen of the tube, it is logical to assume that the use of this intubation aid will predispose to trauma if it does protrude, if it is used blindly and with excessive force.[9]

Pressure on the cricoid cartilage is known to make intubation more difficult in some cases by moving the larynx away from the midline and also, if applied incorrectly, by causing obstruction of the trachea. Increased difficulty with intubation predisposes to airway trauma. Fracture of the cricoid cartilage itself has been reported following rapid sequence induction, which, on extubation, resulted in marked inspiratory stridor, hypoxia and cardiorespiratory arrest. The patient had a previous history of trauma to the larynx that may have predisposed to cricoid cartilage fracture. Although pressures applied to the cricoid cartilage vary widely, even among experienced personnel, and are difficult to measure, it is unlikely that even high pressure could fracture a normal cricoid cartilage.[10]

Experience of an anaesthetist, it was found that presence of blood stain on the endotracheal tube or the natural teeth is associated with increased incidence of POST.[11,12]

Suxamethonium, the role of suxamethonium in the aetiology of postoperative sore throat is unclear. It has been suggested that suxamethonium, which is known to cause postoperative skeletal muscle pain, could also lead to pain in the striated pharyngeal muscles, causing sore throat and hoarseness of voice, this generalized myalgia may last up to 30 hours postoperatively. It is worth mentioning that precurarization was not found to decrease the incidence of postoperative laryngeal complications despite the decrease of incidence of postoperative myalgia.[13]

Endotracheal tube to trachea ratio, and excessive pressure exerted by the endotracheal tube cuff owing to cuff over inflation that may further predispose the patient to postoperative sore throat by causing an increase in the cuff–tracheal contact area or patient's coughing and straining while still intubated during emergence. However, the use of uncuffed tubes was found to be associated with a significantly higher incidence of sore throat than the use of cuffed tubes, even when the patients breathed warmed and humidified gases, as it was thought that this could be due to non-humidified air being drawn across the airway mucosa during spontaneous respiration.[9]

Nitrous oxide, if used, will diffuse into any air-filled space (i.e. air-filled cuffs) and cause significant increase in the intra-cuff pressure particularly in the first hour of anaesthesia.[13]

Filling the cuff with saline, or lignocaine (ETT only) have been shown to be effective methods of eliminating this diffusion and the resulting increase in pressure.[9, 14]

Finally, the lack of use of humidity moisture exchanger, as dry gases use has been implicated as a factor in POST.[15]

**Examples of postextubation laryngeal complications:**

**Sore throat:**

It is a common complication which may contribute to postextubation patients' morbidity and dissatisfaction; it may affect the patients' activities postoperatively. While generally considered a minor side effect it had been rated by the patients as the 8th most undesirable outcome in the postoperative period.[9]

Awareness of the variables associated with an increased incidence of POST can allow providers to minimize combinations of risk factors, in order to reduce the incidence and severity of POST. The method of airway management has been shown to be the most significant predictor of POST, but the selection of an airway device is a multi-factorial decision based upon the patient and the procedure.[16] It may occur with the use of endotracheal tube, supraglottic devices or simple face mask, but it is most common in subjects with endotracheal tube insertion. POST may occur even after a smooth endotracheal intubation.[16,17,18,19] Also it was found that the use of smaller endotracheal tube sizes (7mm for average sized males and 6.5 mm for average sized females) decreases the incidence of POST without any ventilation difficulties.[9]

The reporting of a sore throat is affected by the method of interview, i.e., whether the questions regarding sore throat are asked directly or indirectly. POST (postoperative sore throat) may represent the more specific symptoms of pharyngitis, laryngitis, it was found that the reporting of POST is higher with postoperative nausea and vomiting.[11,15]

Immediate POST may be owing to the action of extubation, while late POST may be owing to the gradual onset of inflammation.[20]

At last, POST is not the most important adverse event to avoid at least from a patient's perspective and it usually resolves within the first 24 hours.[15] Nevertheless, it is an adverse event that could easily be significantly decreased or even potentially eliminated and therapeutic management for decreasing its frequency and severity is still advised to improve the quality of post anaesthesia care even though it may resolve without treatment.[21-23]

**Upper airway obstruction:**

Of all patients undergoing general anaesthesia 2%to 22% will experience increased laryngeal resistance with decreased airflow due to anatomical narrowing of the larynx (oedema) or neuronal imbalance between abductor and adductor nerve supply of the vocal cords. The aetiology of laryngeal oedema in intubated patients is likely pressure and ischemia from the endotracheal tube cuff during prolonged intubation.[23,24]

Depending upon the severity of oedema, patients may go on to develop "A high pitched noisy respiration" known as "Stridor".[25] Stridor is commonly defined as a high-pitched sound produced by airflow through a narrowed airway. The ease of clinically detecting PES (postextubation stridor), without the need for further diagnostic techniques, makes PES a widely used outcome measure for postextubation laryngeal oedema.[24]

Stridor not only leads to anxiety for the patient and the family, but also may progress to acute respiratory failure requiring re-intubation and resulting in increased mechanical ventilation days, ICU days, patients' care costs, morbidity, and mortality. About 15% of all re-intubations which are performed in the intensive care units were found to be owing to postextubation laryngeal oedema.[26] However 50% narrowing is usually reached before respiratory distress develops.[27]

PES is accepted as a clinical marker of laryngeal oedema following extubation. Its reported incidence varies from 3to 30 %.[5,28]

**Catastrophic sequels:**

Early postoperative hypoxaemia may be caused by inadequate minute ventilation, airway obstruction, increased ventilation perfusion mismatch, diffusion hypoxia, post-hyperventilation hypoventilation, shivering, hypoxaemic pulmonary vasoconstriction, mucociliary dysfunction, and a decrease in cardiac output. In a large study involving 24,000 patients, about 1% had a hypoxic event ($S_pO_2 \leq 90\%$) in the PACU requiring intervention other than supplemental oxygen.[29]

The incidence of post-obstructive pulmonary oedema is about 1:1000 anaesthetics; most patients are children or young fit adults. The common pattern is an episode of airway obstruction at emergence followed by rapid onset of respiratory distress, haemoptysis, and bilateral radiological changes consistent with pulmonary oedema.

Both clinical and radiological features usually resolve within 24 hours with no sequels, although delayed presentation of up to 24 hours, progression to acute lung injury and death have also been reported.[30-33] Significant complication rate that does exist is generally attributed to a delay in the diagnosis.[34,35]

Extubation failure is an independent predictor of death.[36] Extubation failure has been defined as "The inability to tolerate removal of the translaryngeal tube" and it is generally treated with tracheal re-intubation.[37]

It was suggested that investigating extubation failure requires "Focusing on the removal of the artificial airway, rather than on the removal of the mechanical support".[38] Noninvasive positive pressure ventilation has been deemed to be a successful therapy after failure of extubation.[39]

Early extubation failure in anaesthesia and ICU patients is commonly due to laryngeal oedema which is generally observed within 1 hour of extubation and rarely observed after 24 hours.[24,40]

Patients who require re-intubation have been noted to have a significantly higher mortality rate than those who are successfully extubated on the first attempt.[28]The reasons for their increased risk of death may include both difficulties encountered during the re-intubation period and the development of additional ventilator related complications, such as pneumonia.[41]

**Postextubation haemodynamic responses:**

Tracheal extubation is associated with a 10–30% increase in arterial pressure and heart rate lasting about 5–15 minutes, patients with coronary artery disease may experience a 40–50% decrease in the ejection fraction.[42]

Coughing is a common airway clinical problem in patients during emergence from general anaesthesia in the presence of endotracheal tube leading to a number of undesirable effects such as agitation, tachycardia, hypertension and increase in the intraocular and the intracranial pressures, which may lead to myocardial ischaemia and bleeding from surgical sites, coughing during emergence may also be associated with broncho- constriction.[43] Tracheal tube and its cuff stimulates rapidly acting irritant receptors in the trachea.[44]Those receptors are assumed to be involved in the cough reflex; the blockade of these receptors by topical application of local anaesthetics may theoretically be a mean of inhibition of cough reflex.[45]

**Management of postextubation laryngeal complications:**

**Non pharmacological management:**

It is not clear how to prevent these problems at extubation, but the problem can be minimized by early intervention to break the upper airway obstruction. Non pharmacological management includes methods that may help to decrease upper airway irritation during emergence from general anaesthesia e.g. extubation with (no touch) technique when the patient is fully awake. This can be done by turning the patient to the lateral (recovery) position and early deflation of the endotracheal tube cuff, only then the inhalational anaesthesia will be discontinued, mechanical ventilation with 100% oxygen will be continued till the neuromuscular block reverse is administrated and return of full muscle power.

Any stimulation to the patient is not allowed as traumatizing oropharyngeal suctioning which may increase the incidence of POST, head turning, pillow removal or any other stimulation which may cause awakening of the patient and increase the incidence of emergence related cough and upper airway irritation. Haemodynamic changes during emergence were found to be significantly less with this technique than with the standard awake extubation.

Deep extubation may also decrease the problem of coughing and straining during emergence but it increases the risk of aspiration and upper airway obstruction due to prolonged timing between extubation and full return of the airway protective reflexes. This is always a great concern in general anaesthesia. Extubation timing is also important, extubation is usually carried out at the end of inspiration when the glottis is fully open to minimize trauma.[43]

It was found that application of water soluble lubricant on the endotracheal tube cuff does not decrease the incidence of POST, but application of a water soluble lubricant on the laryngeal mask airway is recommended as it facilitates its insertion.[46]

Early recognition of laryngeal oedema patients is essential since these patients have the highest risk of evolving to respiratory distress and extubation failure. Even before

extubation, signs indicative of laryngeal oedema may be present. The cuff leak test had gained interest; this test is non-invasive, relatively easy to perform, and it is thought to give an indication of the patency of the upper airway. When the ventilated patient is allowed to exhale with a deflated cuff, expired air normally escapes from the otherwise closed circuit. The volume of leaked air can be measured by spirometric functions of the ventilator. In a case of significant laryngeal oedema, the lumen of the larynx is narrowed. This will result in a smaller measured air leak and the cuff leak test will then be classified as positive.

Miller and Cole made the first attempts to make the cuff leak test quantitative, by measuring the amount of air leak and correlating the cuff leak volume to the likelihood of developing laryngeal oedema and postextubation stridor (PES). They calculated the cut-off value with the highest sensitivity and specificity. Almost none of their study patients with cuff leak volume >110 ml developed PES, the specificity of this cut-off value was 99%, and the sensitivity was 67 %.[47]

**Pharmacological management:**

Pharmacological prophylactic measures for postextubation upper airway problems include anti-inflammatory medications e.g. Non steroidal anti-inflammatory drugs and corticosteroids, which are widely used in clinic. In particular, the inhaled corticosteroids since it can be directly delivered to the airways without introducing a significant systemic exposure with its known side effects. Previous studies have shown that inhalational corticosteroids e.g. budesonide and fluticasone propionate are capable of decreasing the incidence and severity of POST, cough, and hoarseness of voice caused by tracheal intubation.[48]

Corticosteroid administration before extubation is part of the extubation protocol in some centers especially for patients with low cuff leak test volume (<110 ml).[49] As mentioned before, laryngoscopy and moving an airway device may excite sensory C fibers which produces cough and POST. Lignocaine is thought to prevent or suppress the excitation of C fibers and the release of sensory neuropeptides that cause bronchoconstriction.[2]

**Benzydamine:**

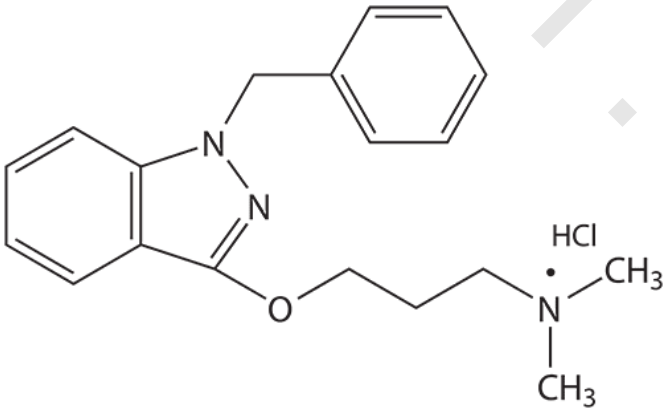


**Figure (1):** Benzydamine Hydrochloride chemical structure.

Benzydamine Hydrochloride chemical structure: {3-(1-benzylindazol-3-yloxy) propyldimethyamine hydrochloride}. It is a locally acting non steroidal anti-inflammatory drug. Benzydamine is derived from indole acid.[50] It has analgesic, antipyretic, antimicrobial, and anti-inflammatory effects.[51]

Benzydamine has an alkaline pH, which means that it becomes concentrated in inflamed tissues and has minimal systemic absorption.[9]

Studies indicate that benzydamine has notable in vitro anti-bacterial activity and also shows synergism in combination with other antibiotics, especially tetracyclines, against antibiotic-resistant strains of Staphylococcus aureus and Pseudomonas aeruginosa.[52] It has a half-life of approximately 8 hours.[53] It is known that benzydamine is rapidly absorbed from the gastrointestinal tract after oral administration, whereas skin and mucosal absorption of the drug is low (<10 percent of the dose) after local application. It is excreted in urine and faeces. BH (benzydamine-hydrochloride) effects last for about two hours.[50]

It had been reported that gross and histological structure of the major organs such as lung, liver, kidney, and spleen were not altered by benzydamine in animal studies.[54]

Its mechanism of action is mediated by the prostaglandin system.[59] It selectively binds to inflamed tissues prostaglandin synthetase inhibitor and is normally free of adverse systemic effects. Also it is suggested that its anti-inflammatory activity is related to its membrane stabilizing effect and inhibition of synthesis of tumor necrotizing factor-alpha. Unlike other NSAIDs, it is not ulcerogenic.[50]

NSAIDS block chemicals that sensitize the primary afferent neuron (PAN) and thereby raise the threshold at which the PAN is transduced. These drugs are powerful analgesics, particularly when there is a tissue injury such as that occurs with excessive oedema.[55]

It has been reported that moderate to severe oral inflammatory conditions may be resolved by gargling benzydamine hydrochloride (BH).[54] In addition, it is widely used in radiation-induced oral mucositis, for arthritis as a gel ointment preparation applied to the skin.[54,56]

Benzydamine has been approved for management of acute sore throat pain.[9] Local spraying of BH can resolve moderate to severe sore throat after endotracheal intubation.[54]Topical application of benzydamine hydrochloride into the oropharyngeal cavity before intubation and its continuous use for 48 hours after the operation has been found to effectively decrease the incidence and severity of POST after endotracheal intubation and also laryngeal mask airway insertion.[56,57]

There are many side effects of topical use of BH, including local numbness, burning or stinging sensation, nausea, vomiting, cough, dry mouth, thirst, drowsiness, and headache. To avoid these drawbacks, it was suggested that the BH should be applicated onto the endotracheal tube cuff instead of into the oropharyngeal cavity, and this may ameliorate the local irritation of BH.[53]

**Lignocaine:**

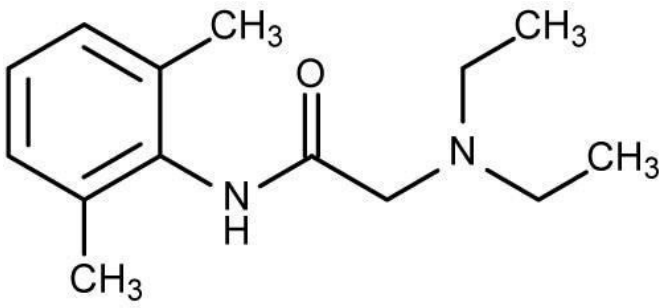


**Figure (2):** Lignocaine chemical structure.

Lignocaine is an amide local anaesthetic which alters signal conduction in neurons by blocking the voltage gated sodium ($Na^+$) channels in the neuronal cell membrane that are responsible for signal propagation.[58] With sufficient blockade the membrane of the postsynaptic neuron will not depolarize and will thus fail to transmit an action potential. This creates the anaesthetic effect by not merely preventing pain signals from propagating to the brain but by stopping them before they begin. Careful titration allows for a high degree of selectivity in the blockage of sensory neurons, whereas higher concentrations will also affect other modalities of neuron signalling. Lignocaine is approximately 95% metabolized (dealkylated) in the liver by CYP3A4 to the pharmacologically-active metabolites MEGX (monoethylglycinexylidide) and then subsequently to the inactive metabolite (glycine xylidide). MEGX has a longer half life than lignocaine but also is a less potent sodium channel blocker.[59] The elimination half-life of lignocaine is approximately 90–120 minutes in most patients. This may be prolonged in patients with hepatic impairment (average 343 minutes) or congestive heart failure (average 136 minutes).[60]

Lignocaine lubricants were found to be ineffective in decreasing POST, and may actually increase the incidence and severity of POST.[61] Lignocaine sprays are consistently associated with an increased incidence of POST. Ethanol, menthol, and polyethylene glycol are common additives to the aerosolized lignocaine, and are thought to worsen POST, lignocaine was believed to be a mucosal irritant in Many studies.[62]

**Fluticasone:**

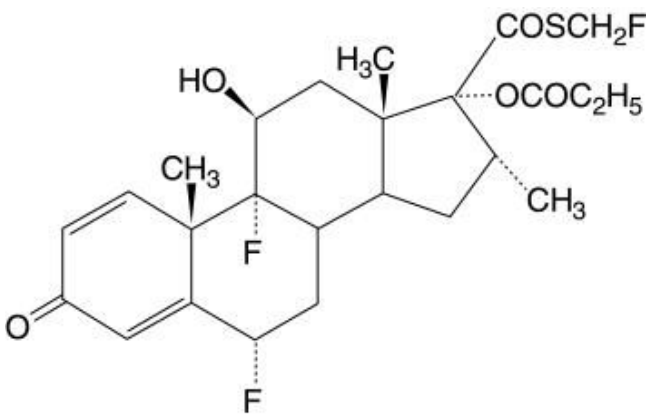


**Figure (3):** Fluticasone propionate chemical structure.

Fluticasone propionate is a synthetic trifluorinated glucocorticoid. It is highly lipophilic and strongly basic with pKa 13.56. Glucocorticoids are naturally occurring hormones that prevent or suppress inflammation and immune responses when administered at pharmacological doses.[63-65]

At the molecular level, unbound glucocorticoids readily cross cell membranes and bind with high affinity to specific cytoplasmic receptors. This binding induces a response by modifying transcription and, ultimately, protein synthesis to achieve the steroid's intended action. Such actions can include an inhibition of leukocyte infiltration at the site of inflammation, interference in the function of inflammatory response mediators, and suppression of the humoral immune responses. Some of the net effects include reduction in oedema or scar tissue and a general suppression in the immune response. The degree of clinical effect is normally related to the dose administered. The anti-inflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, collectively called lipocortins. Lipocortins control the biosynthesis of potent inflammatory mediators such as prostaglandins and leukotrienes by inhibiting the release of the precursor molecule arachidonic acid.[63-65]

Like NSAIDS, the steroids block chemicals that sensitize the primary afferent neuron (PAN) as mentioned before so they are considered powerful analgesics in situations of tissue injury.[63-65]

The numerous adverse effects related to corticosteroids use usually depend on the dose administered and the duration of therapy.[56] The desired properties of inhaled fluticasone propionate include drug delivery in smaller doses and in a shorter time to the patient's airway compared with lubrication of the tube, a high glucocorticoid receptor affinity, a high lung deposition and a long pulmonary residence time , Inhaled fluticasone has been shown to give a more pronounced plasma cortisol suppression after repeated administration than a single dose.[66] This discrepancy between single and repeated dosing for cortisol suppression may be explained by the pharmacokinetic properties of the drug, since fluticasone has been found to have a relatively slow systemic elimination, leading to accumulation and doubling of plasma concentration after repeated dosing.[67] Half-life of fluticasone is considerably longer than for many other inhaled corticosteroids; half-lives in the range of 1.5-2.5 hours have been reported for triamcinolone, acetonide, flunisolide, and budesonide while it has been reported to be 10-14 hours for fluticasone.[67,68]