



## Original Research Article

## Postoperative tracheal extubation- The sequelae

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## ABSTRACT

**Aim:** The frequency of problems related to tracheal extubation probably exceeds those related to tracheal intubation. Our study was undertaken to determine the post extubation sequelae and haemodynamic responses during tracheal extubation.

**Material and Methods:** The study group consisted of randomly selected 250 adult patients in the age group of 18-65 years, belonging to ASA Grade I, II, III, posted for elective surgery under general anaesthesia. We observed the following; Haemodynamic changes [Heart rate (HR), Mean arterial pressure (MAP) changes] and immediate problems associated with post operative tracheal extubation such as bucking, breath holding, cough, airway obstruction, stridor, sorethroat, vomiting, aspiration, pulmonary oedema, residual paralysis occurring during the first 30 minutes of extubation.

**Results:** The changes in HR and MAP were significant soon after extubation ( $p < 0.00$ ) with HR reaching baseline value at 10<sup>th</sup> min ( $p = 0.074$ ) whereas MAP continued to be significant ( $p = 0.032$ ) even at 30<sup>th</sup> min. Incidence of immediate problems associated with postoperative tracheal extubation was 38.4% and these were: Bucking – 26.8%, Breath holding – 4.8%, Persistent cough – 4%, Airway obstruction – 2.4%, Stridor – 0.4%, Sorethroat – 4%, Vomiting – 2.4%. There was no incidence of pulmonary aspiration, pulmonary oedema, residual paralysis.

**Conclusion:** It is concluded that tracheal extubation causes haemodynamic instability and can be associated with detrimental responses.

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## 1. Introduction

Tracheal intubation is reported widely with intense hemodynamic perturbation. Vast literature address the problems associated with tracheal intubation while very few studies have discussed the problems associated with tracheal extubation.<sup>1</sup> Many problems have been discussed with regard to the immediate complications associated with post operative tracheal extubation such as bronchospasm, laryngospasm, cough, stridor, airway obstruction, tracheal collapse, laryngeal oedema, vocal cord paralysis, pulmonary aspiration, pulmonary oedema associated with upper airway obstruction and the unfavourable hemodynamic alterations.

The incidence of respiratory complications associated with tracheal extubation may be higher than that during tracheal intubation.<sup>2</sup>

A great deal has been done to attenuate haemodynamic responses to intubation but the same care and precautions are seldom carried out for extubation. A reliable technique for rapid and smooth extubation is not fully evolved, hence there is an immense need for further study to make extubation a safe procedure, thereby averting clinically detrimental effects.

## 2. Materials and Methods

This study was conducted for a period of 2 years. The study was approved by the institutional ethical committee and

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written informed consent was obtained from patients.

A total of 250 adult patients posted for elective surgery [A variety of elective orthopaedic, general surgery, ENT, gynaecological, neurosurgery and urologic and laparoscopic surgery] under general anaesthesia were selected randomly to be a part of this study. Patients in the age group of 18-65 years and belonging to ASA Grade I, II, III were included in the study. ASA grade IV patients and patients with history of hypertension and cardiovascular disorder were excluded.

Following premedication and preoxygenation with 100% oxygen for 3 minutes, intravenous Lignocaine (1mg/kg), Fentanyl (1 to 2µg/kg), Propofol (1 to 2 mg/kg), Glycopyrrolate (0.01mg/kg), Succinyl choline (2mg/kg), were used to induce the patient. The vocal cords were sprayed with 2 cc of 4% lignocaine before intubation. The following were noted:

1. Number of attempts for tracheal intubation.
2. Any difficulty encountered in intubation process, any use of stylet, bougie etc.
3. Technique of intubation: orotracheal, nasotracheal, retrograde, submental etc.

After intubation the cuff inflation was kept upto 30cmH<sub>2</sub>O

Anaesthesia was maintained with titrated dose of fentanyl and volatile agent of 1 MAC, O<sub>2</sub>:N<sub>2</sub>O ::50:50 and inj vecuronium 0.05mg/kg every 45 min.

After completion of surgery, the residual neuromuscular blockade was reversed with i.v. neostigmine 0.05 mg kg<sup>-1</sup> and glycopyrrolate 0.01mg kg<sup>-1</sup>. Oropharyngeal secretions were suctioned under direct vision before tracheal extubation. Extubation was performed when the patient was adequately awake and train of four (TOF) showed maximum recovery from neuromuscular blockade. After extubation patients received 100% O<sub>2</sub> for atleast five minutes. Patients were observed for problems and complications associated with tracheal extubation such as excessive cough, strido, breath holding, vomiting, residual paralysis, bronchospasm, aspiration and airway edema during extubation and immediate post operative period extending upto 30 min. Parameters monitored were;

1. HR (Heart rate).
2. MAP (Mean Arterial Pressure).
3. TOF (Train of four) measured using peripheral nerve stimulator.

These parameters were documented before giving reversal (baseline intraoperative value), at the time of extubation, 5min, 10 min, 15 min, and 30 min after extubation.

Haemodynamic data [HR, MAP] were recorded using an automated non-invasive BP monitor. ECG was continuously observed for any arrhythmias, ST segment changes. SpO<sub>2</sub> was monitored using the pulse oxymeter. After completion of surgery patients were shifted to the Post Anaesthesia Care Unit (PACU) and observed for 30 min

for any problems. Sore throat was assessed by asking for presence or absence of difficulty in swallowing or unable to swallow.

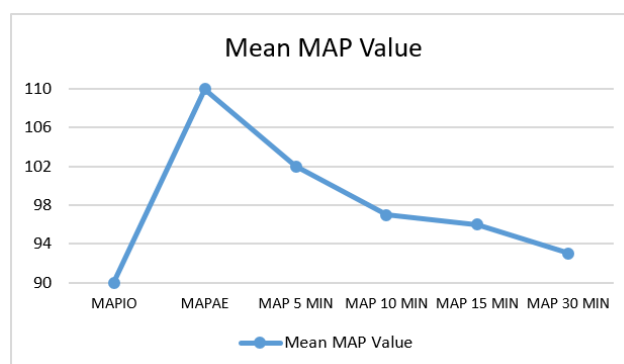
Statistical analysis: The statistical methods employed were, Descriptive statistics, Frequencies, Cross tabs procedure, Repeated measure ANOVA. All the statistical methods were carried out through the SPSS for Windows (version 16.0).

### 3. Results

Demographic data are shown in Table 1.

Among complications observed during post extubation, bucking was most frequently observed in 27% of patients and incidence of stridor being least(0.4%). None of the patients had pulmonary aspiration, pulmonary edema and residual paralysis (Table 2).

The overall incidence of complications encountered following tracheal extubation was 38.4%. There was a maximum increase in both MAP and HR soon after extubation ( $p < 0.00$ ) which decreased over a period of 30mins (Figure 1 and Figure 2). There was more than 20% increase in both HR and MAP soon after extubation, with HR reaching baseline value after 10<sup>th</sup> min of extubation ( $p=0.074$ ) whereas MAP reached close to baseline at 30<sup>th</sup> min after extubation i.e 2% increase, but was still significant ( $p= 0.032$ ) (Table 3)

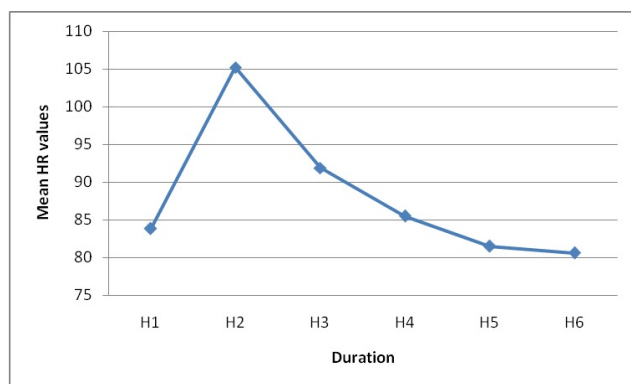


**Fig. 1:** MAP Changes in Post Extubation period (MAP- Mean arterial pressure, MAPIO- intraoperative baseline MAP, MAPAE- MAP after extubation, MAP 5 min- MAP 5 min after extubation, MAP 10 min- MAP 10 min after extubation, MAP 15 min- MAP 15 min after extubation MAP 30 min- MAP 30 min after extubation)

### 4. Discussion

After the “ideal” extubation, patients exhibit adequate ventilatory drive, a normal breathing pattern, a patent airway with intact protective reflexes, normal pulmonary function, and the absence of any mechanical perturbations such as coughing.

Any form of airway dysfunction, such as obstruction after tracheal extubation is an immediate threat to patient



**Fig. 2:** HR Changes in Post Extubation period(HR- Heartrate, H1- HR intraoperative baseline, H2- HR after extubation, H3 - HR 5 min after extubation, H4 - HR 10 min after extubation, H5- HR 15min after extubation, H6-HR 30 min after extubation)

**Table 1:** Demographic variables

	<b>Frequencies</b>
Age subgroups	18-30 yrs – 40.4%, 31-40 yrs - 25.2%, 41-50 yrs - 21.6% 51-60 yrs - 11.2%, > 61 yrs - 1.6%
Gender analysis	Males – 52%, Females - 48%
ASA Grade	ASA I - 63.2%, ASA II - 35.2%, ASA III - 1.6%
Attempts at Tracheal Intubation	1 <sup>st</sup> attempt - 84.4%, 2 <sup>nd</sup> attempt -12.8%, > 3 attempts -2.8%
Difficulty encountered at tracheal intubation	Difficulty in intubation - 8%
Technique of intubation	Oral - 89.2%, Nasal - 9.2%, Submental - 1.6%

**Table 2:** Complications following tracheal extubation

<b>Complications</b>	<b>Incidence</b>
Excessive bucking	26.8%
Breath holding	4.8%
Severe persistent cough	4%
Airway obstruction	2.4%
Stridor	0.4%
Sorethroat	4%
Vomiting	2.4%
Pulmonary aspiration	0
Pulmonary edema	0
Residual paralysis	0

safety. Significant airway compromise leads to diminished minute ventilatory volumes and hypoxemia ensues in a variable, but often rapid fashion.

**4.1. Cardiovascular responses to extubation**

Tracheal extubation is performed usually with the patient in a light stage of anaesthesia and produces significant increase in heart rate and arterial pressure which persist into the recovery period.

The techniques that have been used to diminish the adverse effects of extubation include: extubation in deep plane of anaesthesia, administration of i.v. narcotics, administration of i.v. lignocaine, esmolol, calcium channel blockers, Dexamethasone, suxamethonium, remifentanyl.<sup>3</sup>

Esmolol (1.5-2mg/kg) given as a bolus 2 min after reversal of neuromuscular blockade and Propofol (1mg/kg), administered before tracheal extubation, both have shown to minimize haemodynamic changes and extubation related complications.

Continuous administration of landiolol (0.03 or 0.04 mg kg<sup>-1</sup> min<sup>-1</sup>) may prevent the increases in HR and Rate pressure product respectively, that occur at the emergence from anaesthesia and tracheal extubation.<sup>4</sup>

Mushtaq R et.al studied the cardiovascular responses to tracheal extubation in normotensive patients and compared the same with LMA removal and observed that the parameters studied (HR, SBP, DBP and rate pressure product) increased significantly and was prolonged in patients in whom ETT was used.<sup>5</sup>

A study conducted by Barham N.J. et al revealed that there is a temporal relationship between tracheal extubation and myocardial ischaemia (ST segment changes) in haemodynamically stable patients extubated within 6 hours of cardiac surgery.<sup>6</sup>

In patients with coronary artery disease, the haemodynamic response to extubation may upset the balance between myocardial oxygen supply and demand, resulting in myocardial ischemia. Also the revascularized myocardium may remain vulnerable to anaerobic metabolism in the immediate postoperative period.

In our study, we observed significant haemodynamic change during extubation but none of our patients showed any ischemic changes in the ECG which may be due to strict exclusion of patients with cardiovascular, hypertensive disorders and ASA grade IV patients.

**4.2. Trauma**

Trauma to larynx and vocal cords is particularly likely after a difficult extubation.<sup>1</sup> Damage to soft mucosal structures in the upper airway as a result of excessive suction at the time of extubation should be considered. Dislocation of the arytenoid cartilages has also followed uncomplicated

**Table 3:** Haemodynamic changes following tracheal extubation

Data	Intra operative baseline	Extubation	5 minutes after extubation	10 minutes after extubation	15 minutes after extubation	30 minutes after extubation
HR (Mean +/-S.D)	83.85 +/- 11.9	105.19 +/- 19.44*	91.89 +/-18.70*	85.48 +/-15.71*	81.49 +/-11.86	80.61 +/-11.72
MAP (Mean +/-S.D)	90.73 +/- 10	109.68 +/-13.96*	102.12 +/-11.22*	97.69 +/-8.79*	95.12 +/-9.28*	92.54 +/-8.25**

HR – Heart Rate, MAP – Mean Arterial Pressure

\*- p value < 0.00, \*\*- p value < 0.05 as compared to baseline values

tracheal intubation. It presents as painful swelling and voice change due to glottis edema or acute respiratory failure due to upper airway obstruction immediately after extubation. Voice loss following endotracheal intubation has been reported.<sup>7</sup> Lung laceration with subsequent pneumothorax and lung abscess, after tracheal extubation over a tracheal tube exchanger during which the changer was advanced until a firm resistance was felt, has been described.<sup>8</sup>

#### 4.3. Sorethroat

The hazards inherent to the use of cuffed ETT is the damage inflicted to the trachea in the form of tracheal mucosal ischemia by an over inflated cuff which may also be due to N<sub>2</sub>O diffusion into the cuff.

Complications such as sorethroat, hoarseness and dysphagia occur when the pressure exerted by the cuff on the trachea exceeds the capillary perfusion pressure.<sup>9</sup>

Saline and lignocaine 2% for filling the ETT cuff is an effective means of maintaining cuff pressures during N<sub>2</sub>O anaesthesia, thereby reducing tracheal morbidity.<sup>10</sup> Intracuff pressure is also influenced by anaesthetic depth, degree of muscle relaxation, patient temperature and position, ventilation mode and additional drug administration.<sup>11</sup> The incidence of sorethroat has been reported to be higher in females.<sup>12</sup> The incidence of sorethroat in our study was 4% and it all occurred in cases where we faced a difficult or a traumatic intubation.

#### 4.4. Coughing/Bucking

Coughing frequently occurs during tracheal extubation. Bucking is a more forceful and often protracted cough that physiologically mimics a valsalva manoeuvre. They can cause abrupt increase in intra cavitory pressure i.e increased intracranial pressure, increased intraocular pressure.<sup>13</sup>

Fagan C et.al showed a reduction in the incidence of coughing post extubation when tracheal tube cuff was inflated with 4% lignocaine compared to saline.<sup>14</sup>

Studies show that lidocaine topical spray (5 min prior and during extubation) and lidocaine 1mgkg<sup>-1</sup> i.v (2 min prior to extubation) reduce coughing and haemodynamic response to extubation.<sup>15</sup>

The incidence of excessive bucking at the time of tracheal extubation observed in our study was 26.8% and severe persistent cough following tracheal extubation was in 4% patients.

#### 4.5. Difficult extubation

Causes of difficult extubation may be :

1. Failure to deflate the tracheal tube cuff which may be inadvertent or failure of cuff deflating mechanism due to clipping or kinking or separation of cuff deflating tube.
2. Excessively large cuff catching on the vocal cords.
3. Adhesion of the tube to the tracheal wall.
4. Transfixation of the tracheal tube by a suture.

When there is difficulty in extubation it has been suggested to withdraw tracheal tube under direct vision until the cuff rested against the vocal cords and to deflate by inserting a plastic cannula, or deflate by puncturing the cuff with a needle passed through the cricothyroid membrane when the cuff is at this level.<sup>16</sup>

Inappropriately large tracheal tube or a laryngeal abnormality may lead to difficult extubation in which case rotation of the tracheal tube or manipulation of the larynx and tracheal tube under direct vision may allow successful extubation. Sleeve formation by tracheal tube cuff may lead to difficult extubation in which case reinsertion and inflation of cuff to smooth out the fold or rotation and traction on the tube may allow successful extubation.<sup>17</sup>

In our study, we did not encounter any case of difficult extubation which can be attributed to compulsory use of lubricants for the cuffed endotracheal tubes, and use of appropriate sized tubes (no 7, 7.5, 8 were used in our study).

#### 4.6. Airway Obstruction

Differential Diagnosis of Postoperative Airway Obstruction may be:

1. Laryngospasm
2. Airway muscle relaxation. (Residual muscle relaxants/ Residual anesthetics)
3. Soft tissue edema (allergic reaction/mechanical trauma) - Uvular / Pharyngolaryngeal

4. Cervical hematoma
5. Vocal cord paralysis or dysfunction
6. Foreign body aspiration
7. Consequence of surgery (hemorrhage after thyroid surgery, venous or lymphatic congestion following neck surgery).

In our study, 6 cases of airway obstruction occurred, of which 3 had bronchospasm; One patient was a 55yr old male who underwent open reduction and internal fixation of fracture clavicle. He was obese with short neck. We encountered difficult intubation and we were successful after 3 attempts. Immediately following extubation he presented with difficulty in breathing. On auscultation of the lung fields, there was decreased air entry bilaterally. He desaturated to 70% SpO<sub>2</sub>. Despite management with supplemental O<sub>2</sub> through bag and mask, i.v. and inhalational bronchodilators and steroids, his SpO<sub>2</sub> did not pick up. He was reintubated, paralysed and shifted to the ICU to be put on mechanical ventilator and extubated the next day uneventfully.

Another case of post extubation bronchospasm occurred in a 55 yr old male who underwent laparoscopic procedure for renal cyst. He was a known case of bronchial asthma. He was managed with O<sub>2</sub> supplementation with positive pressure ventilation with bag and mask, i.v. and inhalational bronchodilators and steroids.

Another incidence of severe bronchospasm occurred in a 60 yr old female patient who was an asthmatic, she underwent laparoscopic procedure for malignant ascites. She developed breathlessness 15 minutes following extubation and desaturated. She recovered with i.v. and inhalational bronchodilators and anti inflammatory drugs.

There were three cases of upper airway obstruction; one of the patients had undergone an interval tonsillectomy, and on laryngoscopy for suctioning prior to extubation we observed edema of soft palate and uvula. He developed difficulty in breathing and desaturated following extubation which was probably due to upper airway edema and was managed with supplemental O<sub>2</sub> through ventimask and IV hydrocortisone.

Another case of post extubation upper airway obstruction was a 61 yr old male, who underwent anterior cervical discectomy for Intervertebral disc prolapse C5-C6. He began to gasp for breath after extubation, he had to be reintubated with a smaller sized endotracheal tube, and put on ventilator support in the ICU. He had an uneventful extubation 24 hrs later.

One case of upper airway obstruction occurred in a 39yr old female following extubation, which was probably due to excessive sedation, hence the patient could not maintain her airway. Head tilt and jaw thrust relieved the obstruction and her SpO<sub>2</sub> improved to normal.

#### 4.7. Laryngospasm

It is defined as an occlusion of the glottis by the action of the intrinsic laryngeal muscles. It is less likely to occur when extubation is carried out at the end of inspiration since the firing threshold of neurones supplying the adductors of the vocal cords is increased during inspiration. Laryngospasm reflex is essentially a protective reflex, mediated by vagus nerve, which acts to prevent foreign material entering the tracheobronchial tree.

Laryngospasm is precipitated by local irritation of vocal cords by secretions or blood, and is more likely to occur after tracheal extubation of a patient in a plane of anaesthesia somewhere between an awake and a deeply anaesthetized state where the plane of anaesthesia is insufficient to prevent laryngospasm, but too deep to allow coordinated cough.<sup>18</sup>

Management of laryngospasm is by providing 100% O<sub>2</sub>, deepening the plane of anaesthesia, succinyl choline 0.5 mg /kg and Larson's manoeuvre.<sup>15</sup> Lignocaine 2 mg kg<sup>-1</sup> i.v. and doxapram 1.5 mg kg<sup>-1</sup> i.v. have been reported to be successful. Acupuncture also has been tried successfully.

There were no cases of laryngospasm as our study excluded paediatric patients and extubation was carried out only when the patient was awake and showed adequate neuromuscular recovery and after thorough suctioning.

#### 4.8. Laryngeal oedema

It may be supraglottic, retroarytenoid or subglottic oedema.<sup>12</sup> It is an important cause of upper airway obstruction after tracheal extubation particularly in neonates and infants.

Subglottic oedema produces a significant reduction in the internal laryngeal cross sectional and a 1 mm thick layer of oedema reduces this area to 5 mm<sup>2</sup>(35% of normal). In an adult, this degree of oedema would not cause significant obstruction. Laryngeal oedema presents as inspiratory stridor, usually within 6 hours of extubation. Diminishing stridor may represent impending complete upper airway obstruction rather than resolving oedema.

The incidence of oedema after tracheal extubation of children and the factors contributing to its development includes:

1. Use of a tight fitting tracheal tube.
2. Occurrence of trauma at tracheal intubation.
3. Duration of intubation greater than 1 hr.
4. Coughing on the tracheal tube.
5. Change in position of the patients head and neck during surgery.

Surprisingly, the presence of upper respiratory tract infection was not a significant contributory factor.

Management of Laryngeal oedema includes:

1. Mild cases respond to conservative measures with inhalation of a humidified and warmed O<sub>2</sub> enriched gas mixture.
2. Nebulized adrenaline 1:1000 (0.5 ml/kg upto 5 ml). Relief is dramatic but shortlived.
3. Intravenous dexamethasone 0.2mg kg<sup>-1</sup> immediately followed by 0.1 mg kg<sup>-1</sup> 6<sup>th</sup> hourly for 24 hours has been recommended, although recent studies indicate that dexamethasone was ineffective and rarely reintubation with a smaller tracheal tube may be required.

#### 4.9. Vocal cord paralysis<sup>19</sup>

Vocal cord paralysis resulting from trauma to vagus nerve or its branches is a rare cause of upper airway obstruction after extubation.

Unilateral vocal cord paralysis is a benign condition presenting as hoarseness of voice in early post operative period. Recovery occurs over several weeks. Bilateral Vocal cord paralysis is a more serious condition. It presents as 'upper airway obstruction immediately after extubation.

Vocal cord paralysis is more common with head and neck surgery, and also occurs with increased intracranial pressure. Tracheal intubation may itself result in peripheral nerve damage leading to vocal cord paralysis.

The anterior branches of recurrent laryngeal nerve were found to be susceptible to compression by tracheal tube cuff where they lie beneath the mucosa and immediately medial to the lamina of thyroid cartilage.

Management include immediate insertion of tracheal tube. Recovery is delayed and a tracheostomy may be required temporarily.

In our study, a female patient aged 28 years who underwent total thyroidectomy for papillary carcinoma thyroid, developed difficulty in breathing and inspiratory stridor with desaturation following extubation. Patient was reintubated nasally and connected to T-piece and supplementary O<sub>2</sub>, and after 3 days patient was extubated under fiberoptic laryngoscopy vision, bilateral vocal cords mobility was restricted and right arytenoids submucosal hematoma seen which gradually resolved over a period of 1week.

#### 4.10. Tracheal collapse

Can be a cause for post extubation stridor (PES). Studies have demonstrated that Cuff Leak Test failure is not an accurate predictor of PES and should not be used as an indication for either delaying extubation or initiating other specific therapy. Female patients, those whose ratios of ETT size to laryngeal diameter was >45% and patients intubated for 6 days are more likely to develop PES.<sup>20</sup> In our study not observed any case.

#### 4.11. Laryngeal incompetence<sup>21</sup>

Protective laryngeal reflexes are obtunded by residual effects of anaesthetic agents. Laryngeal function is disturbed for atleast 4 hrs after tracheal extubation even in alert postoperative patients and there is risk of aspiration of foreign material. Best protection against pulmonary aspiration is obtained by pharyngeal suction under direct vision, followed by extubation in lateral position with head down tilt.

#### 4.12. Pulmonary edema associated with upper airway obstruction

The pathogenesis of the pulmonary oedema is multifactorial, although the markedly negative intrathoracic pressure generated during an episode of acute upper airway obstruction is probably the dominant pathophysiological mechanism. The onset of pulmonary oedema is usually within minutes of either development of acute upper airway obstruction or after relief of obstruction. Resolution usually occurs spontaneously over a period of few hours.

Management includes airway maintenance by tracheal intubation, supplementary oxygen administration, and if necessary, institution of positive pressure ventilation until condition resolves. Medical management includes, furosemide 10-40 mg I.V., morphine 5-10 mg I.V. to decrease venous return to the heart.<sup>22</sup>

#### 4.13. Tracheal stenosis

There is lack of association between duration of endotracheal intubation and tracheal injury, instead excessive amount of movement or writhing while intubated is known to lead to tracheal stenosis.<sup>23</sup>

#### 4.14. Residual paralysis

Complete recovery of neuromuscular function should be present at the time of tracheal extubation to reduce the risk of adverse respiratory events.<sup>24</sup>

Inadequate reversal may still be present when there is spontaneous ventilation. The TOF ratio that is judged to be adequate is as high as 0.9. Recent studies have demonstrated that respiratory and pharyngeal function do not normalize until TOF ratios of 0.8- 1 are obtained. Eikermann et al.<sup>25</sup> observed that impaired inspiratory flow and upper airway obstruction occurred frequently at a TOF ratio of 0.83.

In our study there have been no cases of residual paralysis probably due to the use of neuromuscular monitoring and extubation was performed only when TOF showed maximum recovery.

#### 4.15. Extubation of the difficult airway.

Re-establishing and securing the airway in difficult airway patients can be extremely challenging, often resulting in

undesirable morbidity and mortality.

Feasibility of extubation is commonly determined by direct laryngoscopy and cuff leak before extubation to detect oedema around the airway. Airway exchange catheters, jet ventilation, Fiberoptic bronchoscopy may be lifesaving. Use of tube exchangers mandates familiarity with the technique to minimise complications.<sup>26</sup>

DAS (Difficult Airway Society) extubation guidelines 2015 provide algorithms for safe management of tracheal extubation in adult perioperative practice.

## 5. Conclusion

Extubation under deep plane of anaesthesia can delay recovery and that under light planes of anaesthesia carries the risk of excessive coughing, bucking, haemodynamic changes. Judging when to extubate is best learnt through experience, the risks are overcome by anticipation and devising appropriate management strategy.

## 6. Source of Funding

None.

## 7. Conflict of Interest

None.

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