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Effects of Dexamethasone on Laryngeal Edema following Short-Term Intubation

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Following short-term intubation for general anesthesia, respiratory difficulty may result from laryngeal or subglottic edema after extubation. We have hypothesized that this problem could be pretreated by administering a high-dose of dexamethasone intravenously before extubation.

After glottic injuries were made under direct laryngoscopic view, intubation was performed and maintained for 1 hour in 33 rabbits. The rabbits were divided into 3 groups; dexamethasone(1 mg/kg) was administered to group 1(n=12) immediately after intubation and group 2(n=10) just before extubation; group 3(n=11) received normal saline, just before extubation. After extubation, subglottic excursion pressure was measured for 4 hours. 15 injured rabbit larynges and 3 normal ones, were extracted for histologic section.

2 of 12 rabbits in group 1; 3 of 10 in group 2; and 5 of 11 in group 3, showed mild stridor after extubation($p>0.05$). All rabbits developed maximum increase in subglottic pressure within 2 hours after extubation. Group 1 and 2 showed less increase in pressure compared to group 3($P<0.05$), but there was no statistical difference between group 1 and 2($P>0.05$).

Histologic sections of the larynges showed less submucosal edema, including other changes in group 1 and 2, than in group 3($P<0.05$). In conclusion, administering a high-dose of dexamethasone before extubation, is effective in prophylaxis and treatment of laryngeal injuries following short-term intubation in rabbits. This is especially true in edema.

Key Words: Acute laryngeal edema, intubation, dexamethasone, rabbit

Laryngotracheal injury during surgery under anesthesia has been one of the major concerns of the anesthetists and laryngologists, but most discussion has centered around the sequelae of prolonged intubation. Since the dangers of intubation begin with the insertion of the tube, the possibility of significant laryngeal injury may be followed by short-term intubation. Short-term endotracheal intubation and rigid bronchoscopy can cause laryngeal or subglottic edema combined with epithelial sloughing and inflammation following the procedures. The edema can result in post-extubation respiratory problems, especially in children. The frequency of clinical respiratory symptoms is highly variable, ranging from very low, following short-term intubation in elective surgical children and adults, to 37% following intubation for burns or trauma in children(Goddard *et al.* 1967; Koka *et al.* 1977; Kambic and Radsel, 1978; Peppard and Dickens, 1983).

Clinically, corticosteroids are commonly used to hasten the resolution of post-traumatic laryngeal edema, but there are few adequate experimental and clinical studies supporting

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their use.

The purpose of this study was to establish an experimental model, in rabbits, of acute traumatic laryngeal edema and to evaluate the effect of pre-treated corticosteroids as a prophylaxis, as well as for treatment.

MATERIALS AND METHODS

An experimental model for laryngeal edema was developed with the use of white New Zealand rabbits. Rabbits were selected because their upper tracheal wall consists of a mucous membrane and a series of horse-shoe shaped cartilage of the same appearance as in the human trachea(Nordin *et al.* 1977). Also their larynges are approximately the size of a child' s larynx, and they are reliable animals for laboratory study.

33 rabbits, each weighing 1.6~2.5 kg, were used. They were divided into 3 groups, 12 treatment-1 rabbits(group 1): 10 treatment-2 rabbits(group 2): 11 untreated rabbits(group 3).

Ketamine hydrochloride was given intramuscularly to induce anesthesia. After electrodes were attached for ECG monitoring, the auricular artery and marginal vein were cannulated for blood pressure monitoring and continuous infusion of anesthetics. The cervical trachea was exposed in the study groups using an ID 4.0~4.5 cuffed endotracheal tube (Mallinckrodt, Mallinckrodt Laboratories) under direct larygoscopy. Friction was made by entering and exiting the glottic entrance 4 times. Intubation was then performed and the cuff was inflated at a pressure of 100 mmHg. The cuff was placed just below the vocal cords.

After 1 hour of intubation the endotracheal tube was removed and the subglottic excursion pressure was measured via a 20 G polyethylene tube inserted into the subglottis through the exposed cervical trachea. The excursion pressure was recorded by polygraph (Grass 79E, Grass Medical Instruments) continuously for 4 hours. Three different experiments were conducted.

1) 12 rabbits were given 1 mg/kg of dexamethasone phosphatate intravenously just after intubation(group 1).

2) 10 rabbits were given the same dosage of dexamethasone just before extubation(group 2).

3) 11 rabbits were given same volume of normal saline just after intubation(group 3).

During subglottic excursion pressure measurement, the tongue was pulled out of the oral cavity to avoid mechanical obstruction and oxygen was given via oral airway.

Of 33 rabbits, only 15 rabbits in body weight 2~2.2 kg were selected for histologic evaluation of larynges. Larynges were excised after the rabbits put to sleep and exsanguination was done. The larynges were fixed in a 10% formalin solution, then embedded in paraffin. Several sections from the larynx and sub-glottis were cut at 2 micrometer thickness and processed for hematoxyline and eosin staining. Histologic analysis was made by a pathologist using a scoring system to whom the experimental grouping was unknown. Statistics were established using the Chi-square test for comparison of incidence of stridor among the groups and the Mann-Whitney U-test used between groups when there was a significance in the Kruskal-Wallis test for histologic findings. P values of less than 0.05 were considered significant.

RESULTS

Although clinical observation showed that mild stridor developed in 2 of 12 rabbits in group 1, 3 of 10 in group 2, and 5 of 11 in group 3 after extubation, significant difference was not showed among three groups($P>0.05$). All rabbits developed maximum increase in subglottic excursion pressure within 2 hours following extubation(Fig. 1). The excursion pressure declined gradually after 2 hours, and the subglottic pressure reduced to near baseline value 4 hours after extubation in dexamethasone pretreated groups, but not in the untreated group. The rabbits that received dexamethasone(group 1) immediately after intubation showed a smaller increase in pres-

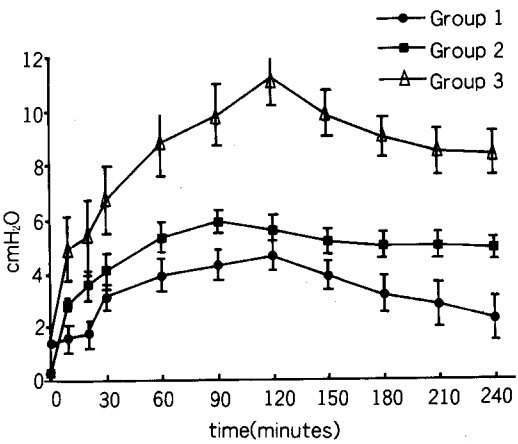

Fig. 1. *Subglottic pressure changes by time after extubation.*
**: Maximal increase in subglottic excursion pressure after extubation*

sure compared to the untreated group(group 3) and the rabbits that received steroids just before extubation(group 2). However, there was no significant difference between group 1 and 2.

Histologic sections of the larynges after 4 hours post-extubation showed less changes of, epithelial sloughing, proliferation, submucosal edema, and inflammation in the dexamethasone treated rabbits than in the untreated group(Table 1).

Table 1. The histologic comparisons of three groups

Group	Epithelium		Submucosa	
	Sloughing	Proliferation	*Edema	Inflammation
1(n=5)	1.2 (0~2)	1.6 (0~3)	1 (1)	1.5 (1~2)
2(n=4)	0.25(0~3)	2.5 (1~3)	1.25(1~2)	1.25(0~3)
3(n=4)	2 (2~3)	3.25(3~4)	2.25(2~3)	1.75(1~2)

*:P<0.05 by Mann-Whitney U-test

Histologic analysis was made using a scoring system(0: no changes, 1: mild changes, 2: moderate changes, and 3: severe changes).

DISCUSSION

The findings of this study show that a severe laryngeal and subglottic edema could be produced from short-term placement of an endotracheal tube with a highly pressurized cuff and that a high dose of dexamethasone(1 mg/kg) could be used to improve the laryngeal and subglottic edema that results. Also corticosteroids could be used to decrease other inflammatory changes.

The measurement of changes of subglottic excursion pressure accurately reflect the laryngeal obstruction secondary to edema. The occurrence of edema was rapid with all rabbits showing maximal laryngeal obstruction within 2 hours post-extubation. Comparatively however it was slower than the monkey model(Biller *et al.* 1970) and faster than the ferret model(Wood *et al.* 1987; Kryzer *et al.* 1991).

Acute glottic and subglottic injury with subsequent edema may cause significant airway narrowing resulting in a respiratory problem after extubation; presenting stridor, suprasternal retraction, and croupy cough. Children are most susceptible to these problems. Of the larynx, the vocal process of the arytenoid and the posterior aspect of cricoid cartilage are the highest risk area to this kind of injury. Mucosal damage is caused by a combination of pressure or friction by an endotracheal tube and the dynamic effects of the tube itself(Bishop *et al.* 1984; Wood *et al.* 1987). If the submucosal edema occurs on the surface of the epiglottis, aryepiglottic folds, or both, the glottic opening will be impinged upon and if the edema occurs in the retroarytenoid area, the abduction of vocal cords will be limited on inspiration. Either condition may cause marked ventilatory obstruction. Sometimes, submucosal edema may lead to ischemia, ulceration, secondary infection, perichondritis, and eventually subepithelial fibrosis with granulation tissue(Blanc, 1974). Therefore, it is important to either prevent edema, if possible, or treat it upon onset as early as possible.

Brushing technique is commonly used to make a laryngeal injury in an animal(Kryzer *et al.* 1991), but it may induce severely compromised results compared to an actual short-term intubation. We have developed a laryngeal injury model in rabbits as a manner of short-term intubation or rigid bronchoscopy, by causing friction against a tube under direct laryngoscopic view.

Steroids are known to induce a decrease in laryngeal edema and acute inflammatory phase of injury by inhibiting the influx of inflammatory cells and limiting the capillary endothelial permeability(Deming and Oech, 1961; Cobb and Sudderth, 1972; Croft *et al* . 1979). Other animal studies show that steroid therapy needs to be instituted early in the course of the inflammatory process(Croft *et al.* 1979; Kryzer *et al.* 1991). In a clinical setting, there are still many arguments whether steroid administration is beneficial or not for prophylaxis and treating acute laryngeal injury (Gaussorgues *et al.* 1987; Ferrara *et al.* 1989; Super *et al.* 1989). However, in terms of acute edema, the use of steroids are strongly recommended. Steroids are usually given at the time of extubation. Before we began this study, we hypothesized that administration of high doses of steroids immediately after intubation might be more effective in reducing laryngeal edema than giving it at the time of extubation because the maximal effects of dexamethasone occurred between 1 and 2 hours, although Goddard *et al.*(1967) demonstrated in a double-blind study that prophylactic administration of betamethasone(0.2 mg/kg, equivalent anti-inflammatory potential as dexamethasone) did not reduce the incidence of postintubation inflammation in children after general anesthesia. Biller *et al.*(1970) demonstrated large dose dexamethasone(4 mg/kg) administration at the time of extubation to be useful for pro-phylaxis against subglottic edema after intubation in monkey model.

Histologic sections of the larynges through glottis indicated less mucosal and submucosal injuries in the treated groups than in the untreated group(Fig. 2-4). Although the edema is

Fig. 2. *Mucosal and submucosal findings of vocal cord area of rabbit administered dexamethasone immediately after intubation(H&E, ×400).*

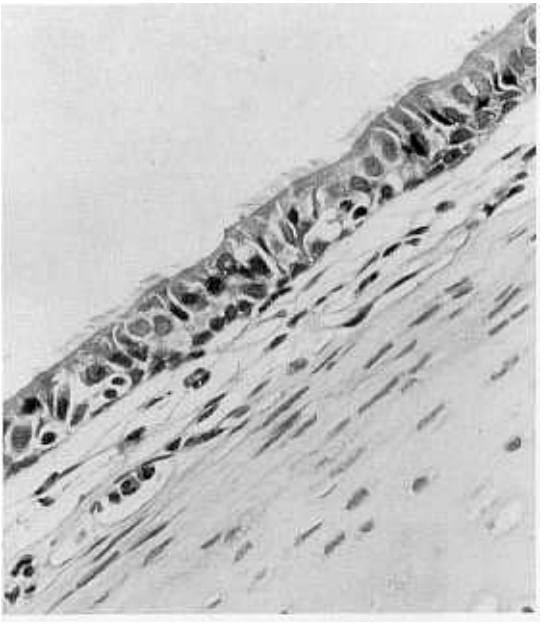

Fig. 3. *Mucosal and submucosal findings of vocal cord area of rabbit administered dexamethasone just before extubation(H&E, ×400).*

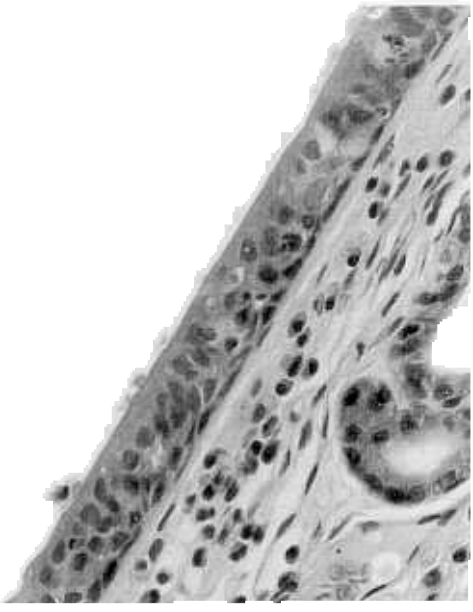

Fig. 4. Mucosal and submucosal findings of vocal cord area of untreated rabbit. Note the epithelial sloughing, submucosal edema, and poly cells(H& E, × 400).

difficult to quantitate histologically, the increased subglottic pressure is due to glottic edema and the clinical implication is correlated to histologic results. However, there was no definite difference between steroid groups 1 and 2 and we can not suggest that the preadministration of dexamethasone is more efficacious against acute laryngeal edema following short-term intubation than administration of it at the time of extubation.

In this experimental study, subglottic pressure measurements reflected accurately the degree of laryngeal obstruction secondary to acute edema following short-term intubation. Administration of high doses of dexamethasone(1 mg/kg) before extubation is effective as a prophylaxis and treating traumatic mucosal and submucosal changes of larynx, especially in edema. These results may have clinical implications in the treatment of subglottic injury following short-term intubation and rigid bronchoscopy in children by reducing acute phase edema. However, we cannot suggest that administration of steroids immediately after intubation is more efficacious against the laryngeal edema than administration of it at the time of extubation.

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