ORIGINAL ARTICLE

ROLE OF DEXAMETHASONE FOR PREVENTION OF POST-EXTUBATION AIRWAY OBSTRUCTION IN CRITICALLY ILL ADULT PATIENTS

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ABSTRACT

Objective — *To evaluate whether dexamethasone started 24 hours prior to planned tracheal extubation in adults, can prevent post-extubation laryngeal oedema.*

Study design — *Randomized placebo-controlled double-blind trial.*

Place & Duration of study — *Department of Anaesthsiology, Surgical ICU and Pain Management, Jinnah Postgraduate Medical Centre Karachi, from August 2006 to July 2008.*

Methodology — *Ninety-two patients who met weaning criteria after being intubated for more than 48 hours, with a cuff leak volume (CLV) of less than 110 ml were randomly allocated to two groups; receive either intravenous dexamethasone (5 mg) or identical volume of intravenous placebo (normal saline), and continued every six hours thereafter, for a total of four doses (total dose 20 mg) on the day preceding extubation. Cuff leak volume was measured at the time of the first injection, and one hour after each injection and 24 hours after the last injection. Patients were extubated twenty-four hours after the last injection of dexamethasone or identical volume of intravenous placebo. Occurrence of stridor was noted within 48 hours of extubation.*

Results — *Dexamethasone injection 24 hours prior to extubation increased the CLV significantly (P=0.001). Post-extubation stridor was 54.6% significantly lower in the dexamethasone group than in placebo group (6/46 versus 15/46, P=0.025).*

Conclusions — *Dexamethasone given every six hours intravenously, commencing 24 hours before a planned tracheal extubation, substantially reduced the incidence of post-extubation stridor and re-intubation, in adult patients at high risk for post-extubation laryngeal oedema, as identified by the cuff leak test.*

Key words — *Dexamethasone, Tracheal extubation, Cuff leak test.*

INTRODUCTION:

Experimental and clinical investigations have consistently shown that endotracheal intubation can lead to laryngeal and tracheal mucosal oedema, inflammation and ulceration, in particular at the level of vocal cords and site of endotracheal cuff. Laryngeal trauma, found in a large proportion of Intensive Care Unit (ICU) patients at the time of extubation, has been observed as early as three to four days after tracheal intubation, and may require several weeks to resolve.[1]

Laryngo-tracheal injury related to intubation may cause narrowing of the airway mainly due to inflammatory oedema. The potential capacity of steroids to relieve laryngeal oedema is mainly due to its anti-inflammatory effects, which inhibit the release of inflammatory mediators and decrease capillary permeability. The initial anti-inflammatory effects start at least one to two hours after intravenous administration and maximal effects

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appear between 2 and 24 hours, depending on steroid type and administered dose.[2,3]

Laryngeal oedema is clinically defined as the development of upper airway obstruction after extubation, and further classified as minor or major. Minor laryngeal oedema is defined as evidence of stridor associated with respiratory distress requiring medical intervention. Major laryngeal oedema is defined as severe distress prompting tracheal re-intubation and confirmed with direct visualization by laryngoscopy. Thus, prevention of post-extubation laryngeal oedema has been the focus of considerable research effort. There is biologic plausibility and rationale to use corticosteroids for this indication.[4]

Post-extubation stridor associated with post-extubation laryngeal oedema is one of the most frequent causes of re-intubation in the ICU. Re-intubation may result in increased morbidity (for example, nosocomial infection, prolonged length of ICU stay, additional costs) and mortality.[2] The ability to predict which patients will develop stridor following extubation, possibly culminating in re-intubation, is obviously a desirable goal. Beyond assessment of risk factors, clinicians have long used the cuff-leak test to predict post-extubation airway patency, wherein the endotracheal tube cuff is deflated and a leak of air around the tube is sought during either spontaneous ventilation (with the endotracheal tube lumen occluded) or positive pressure ventilation.[2] Cuff leak test studies suggest that the pressure of an air leak is associated with a low likelihood of clinically important post-extubation stridor, whereas the absence or a low level of leak (less than 110) is associated with a high incidence of stridor and reintubation.[2,5]

This study was conducted to assess the usefulness of steroids in facilitating tracheal extubation in an ICU setting.

METHODOLOGY:

The study included patients who were admitted to the Surgical Intensive Care Unit of Jinnah Postgraduate Medical Centre, Karachi between August 2006 and July 2008 and who met the inclusion criteria described below. Informed consent was obtained from the patients or their relatives. This study was approved by the Medical Research Ethics Board.

Inclusion criteria were adult patients (age >18 years) who were scheduled for planned tracheal extubation after having received mechanical ventilation for >48 hours and met all the weaning criteria. The exclusion criteria were administration of corticosteroids one week prior to extubation during the same hospitalization, pregnancy, history of post-extubation upper airway obstruction, primary ICU admission diagnosis of throat disease or surgery, tracheostomy, and those who had been chronically treated with non-steroidal anti-inflammatory drugs or corticosteroids. All patients were intubated with a high volume, and low pressure cuffed endotracheal tube (ETT) with an internal diameter of 7.0, 7.5, and 8.0 mm. If required, patients were sedated or paralyzed during mechanical ventilation. Periodic ETT suctioning was done as needed to maintain patency of the airway. Cuff leak test was administered to the patients who required mechanical ventilation for more than 48 hours and who fit in the above inclusion criteria. Cuff leak volume (CLV) was determined as the difference in the actual tidal volume before and after cuff deflation.

Patients requiring mechanical ventilation for more than 48 hours and exhibiting a CLV of less than 110 ml before planned extubation were included in the study. Cuff leak volume of less than 110 ml has been determined as a predictor of postextubation stridor.[5] The intubation was performed by the attending resident. Patients were randomly allocated to receive either dexamethasone or placebo. Allocation was stratified by site, and was concealed in sequentially numbered sealed opaque envelopes. Patients were allocated to either intravenous dexamethasone or placebo, 24 hours prior to planned tracheal extubation and continued every six hours, for a total of four doses on the day preceding extubation.

Cuff leak volumes were measured for two groups, namely steroid group and placebo group before the first injection, one hour after each injection for a total of four doses. Patients were extubated 24 hours after the last injection of dexamethasone or placebo. The primary endpoint was occurrence of laryngeal oedema within 24 hours of planned tracheal extubation.

Post-extubation obstruction was recorded. Those patients, who exhibited high pitched wheeze, were given epinephrine inhalation and those with respiratory distress were given non-invasive positive-pressure ventilation (bi-level positive airway pressure). Patients were reintubated and put on mechanical ventilation if they had a change in mental status and were not tolerating noninvasive ventilation or had a pH of less than 7.3 with an increase in $paCO_2$ of more than 15 mmHg or hypoxemia with PaO_2 of less than 50 mmHg with an FiO_2 of more than 70%, or signs of respiratory muscle fatigue and copious secretions.

The data was analyzed on SPSS version 15.0. The mean difference of quantitative variables like age, weight, duration of intubation, diameter of ETT, GCS and cuff leak volume were compared by t-test for two

independent samples. For qualitative variables like gender and complications, the Chi-square test of independence or Fisher's Exact test were employed. The results was considered significant at P<0.05.

RESULTS:

Three hundred and twenty patients were made to undergo cuff leak volume test. Two hundred had a CLV of more than or equal to 110 ml and were therefore extubated. Twenty patients were excluded seven because of self extubation and thirteen had deteriorated clinical condition. Hundred patients with a CLV of less than 110 ml met the inclusion criteria. The patients were randomly assigned into the dexamethasone group (n=50) and the placebo group (n=50). In the dexamethasone group, two patients withdrew due to respiratory failure and two due to self extubation. In the placebo group, two patients withdrew due to respiratory failure and two due to pulmonary oedema. The final inclusion of patients in two groups viz dexamethasone group and placebo group were 46 patients each.

The dexamethasone and placebo groups did not significantly differ in the demographic characteristics, including age (years), weight (Kg), duration of intubation (hours), diameter of ETT (mm), GCS, underlying disease and severity of illness (table 1).

At the time of first injection, there was no significant difference of mean CLV (ml) between steroid and placebo groups (P=0.085). One hour after second injection at six hours, the difference in CLV was found highly significant between two groups with P=0.001, and having a percentage difference of 44.20% from steroid to placebo group. The same trend was consistently noted after each injection of dexamethasone. One hour after fourth injection, the CLV raised from 55.09±7.6 ml at the first injection to 117.28±3.31 ml in the steroid group whereas, in placebo group, it did not show any significant change and only raised from 52.52±6.19 to 53.23±5.13 at one hour after fourth injection (table 2).

The incidence of post-extubation stridor was 21 out of 92 (28.8%). Six out of 21 (28.5%) in the dexametasone group and 15 out of 21 (71.5%) in the placebo group. The incidence of stridor in two groups was found statistically significant with p=0.005, Chi-square 7.71. The relative risk of stridor in placebo group was 51% as compared to dexamethasone group (table 3). Reintubation with mechanical support was necessary in 2 of 46 patients (4.3%) in the dexamethasone group and 9 out of 46 (19.5%) in the placebo group (p=0.045).

Table I: Demographic variables with ETT Internal Diameter (mm), Mechanical Ventilation Time (Hours) and GCS

Variables	Steroid Group (n=46)	Placebo Group (n=46	p-value
Male	27	0	0.65(ns)
Female	19	22	
Age (years)	38.72 ± 12.3	40.57 ± 12.99	0.48 (ns)
Weight (Kg)	64.71 ± 7.59	63.91 ± 6.75	0.59 (ns)
Hb (gm/dl)	9.55 ± 0.41	9.49 ± 0.38	0.53 (ns)
ETT internal diameter (mm)	7.61 ± 0.49	7.47 ± 0.53	0.44 (ns)
Mechanical Ventilation time (hours)	71.37 ± 12.84	70.58 ± 8.97	0.22 (ns)
GCS	12.73 ± 1.61	12.78 ± 1.86	0.73 (ns)

Table II: Cuff Leak Volume (ml) at Different Duration

Cuff Leak Volume (ml)	Steroid Group (n=46)	Placebo Group (n=46)	P-value	% Difference from Steroid Group to Placebo Group
At the time of 1st injection	55.04 ± 7.6	52.52 ± 6.19	0.085	4.58%
One hour after 2nd injection at 6 hours	93.08 ± 5.81	51.86 ±5.39	0.001	44.20%
One hour after 3rd injection at 12 hours	102.21 ± 14.84	53.00 ± 5.11	0.001	48.15%
One hour after 4th injection at 18 hours	117.28 ± 3.31	53.23 ± 5.13	0.001	54.61%

Table III: Complications in Steroid and Placebo Groups

Complications	Steroid Group (n=46)	Placebo Group (n=46)	P- value*	Relative Risk
Postextubation stridor (n=21)	6	15	0.025	51%
Nebulization+biPAP (n=21)	6	15	0.045	44%
Reintubation and ventilation (n=21)	2	9	0.045	51%
*Steroid Group vs Placebo Group				

During our study, no patient exhibited GI bleeding, altered haemodynamics, nosocomial infection, hyperglycemia, arterial hypertension and agitation.

DISCUSSION:

The potential benefit of steroids to laryngeal oedema is presumably based on its anti-inflammatory actions, which inhibit the release of inflammatory mediators and decrease capillary permeability. The risk of harm from steroid therapy for 24 hours or less to prevent postextubation laryngeal oedema is negligible.[6] The extent of the effect of prophylactic steroids on airway obstruction is still a matter of some controversy.[3]

Observational studies suggest the incidence of post-extubation laryngeal edema in ICU patients, characterized by stridor and/or respiratory distress, ranges from 4-22% depending on the specific population being investigated.[5,7] Numerous factors have been associated with a higher risk for post-extubation stridor in ICU patients, including female sex, large ratio of endotracheal tube size to laryngeal size, traumatic and/or difficult intubation, history of self-extubation, longer duration of intubation, higher severity of illness, non-surgical admissions, and a primary diagnosis of head/neck trauma.[5,8] In addition, a low absolute cuff leak volume (<110-130 ml) and/or a high proportion of deflated to inflated expired tidal volume (<10-12%) have also been correlated with a higher likelihood of post-extubation stridor.[5,9]

Roberts et al compared trials published after 2000 with older studies,[10] and suggested that the lack of clinical benefit observed with earlier studies might have resulted from lower total steroid doses. Those authors also pointed out that older studies generally used a single dose of steroids and suggested that this, compared with longer duration of treatment in newer studies, might account for the different conclusions. Tao Fan et al in a meta-analysis found dose dependent effects in multiple dose regimens but not in single dose regimens, steroids are usually administered at least 12 hours before extubation and repeated almost every plasma half life. This might maintain a high level of anti-inflammatory activity during the period of vulnerability to oedema after extubation. Although steroids have several potential adverse events, particularly in patients already at risk of hyperglycemia and complications of infection, side effects with steroid treatments over 24 hours are minimal.[11]

In a study on unselected adult patients, a 8 mg injection of dexamethasone given one hour before extubation did not reduce the number of patients requiring reintubation.[7]

To determine whether corticosteroids are effective in preventing or post extubation stridor in critically ill infants, children or adults in a Cochrane Database Syst Rev in 2008, it was concluded that there is a trend towards a reduced incidence of re-intubation in neonates receiving prophylactic dexamethasone prior to extubation. In children, prophylactic administration of dexamethasone prior to elective extubation reduces the incidence of post extubation stridor, but the evidence is insufficient to conclude that rates of re-intubation are reduced. In adults, corticosteroids do not appear to reduce the need for re-intubation.[12]

In Cochrane Detabase Syst Rev 2009, the authors concluded that using corticosteroids to prevent (or treat) stridor after extubation has not proven effective for neonates or children. However, given the consistent trends towards benefit, this intervention does merit further study, particularly for high risk children or neonates. In adults, multiple doses of corticosteroids begun 12-24 hours prior to extubation do appear beneficial for patients with a high likelihood of post extubation stridor.[13]

In a meta-analysis by Tao Fan et al,[11] randomized placebo controlled trials were included comparing the prophylactic administration of steroids versus placebo before planned extubation in adults, with adequately reported data on either the occurrence of laryngeal oedema after extubation or the rate of consequent reintubation. On currently based evidence, this meta-analysis strongly suggested that prophylactic administration of parenteral steroids in a multidose

regimen before planned extubation is effective in reducing the global incidence of laryngeal oedema and subsequent need for reintubation, with few adverse events.

We conducted this trial to evaluate the effects of prophylactic dexamethasone therapy in preventing laryngeal oedema for adult patients with CLV of less than 110 ml in Surgical ICU setting. The endotracheal tube (ETT) cuff-leak test (CLT) has been proposed as a relatively simple, noninvasive method for detecting the presence of laryngeal oedema prior to tracheal extubation.[8] Dexamethasone was selected because of its high anti-inflammatory property and minimal mineralocorticoid effects at therapeutic doses, and long duration of action.[14]

Our results showed significant difference of post extubation stridor (28.5% in dexamethasone group and 71.5% in placebo group) and reintubation (4.3% in dexamethasone group and 19.5% in placebo group). Cuff leak volume significantly increased in the dexamethasone group. It was noted that the effect of multiple dose dexamethasone in increasing CLV occurred not only throughout the treatment period, but also during the observation period of next 24 hours.[6]

Our findings of steroid effects in reducing post-extubation stridor were consistent with a study by Francois and colleagues who reported that methylprednisolone 20 mg given intravenously every four hours, commencing 12 hours before a planned tracheal extubation substantially reduced the incidence of post-extubation laryngeal edema and rate of re-intubation.[6]

CONCLUSIONS:

Dexamethasone, a long acting and potent corticosteroid, is suitable for preventing post-extubation airway oedema. Administration of multiple prophylactic doses of dexamethasone significantly decreases the incidence of post-extubation stridor in adult patients at high risk to develop airway obstruction. The after-effect of dexamethasone may validate the reduced incidence of post-extubation stridor after multiple-dose dexamethasone.

REFERENCES:

1. Colice GL. Resolution of laryngeal injury following translaryngeal intubation. Am Rev Respir Dis 1992; 145:361-4.

2. Jaber S, Jung B, Chanques G. et al. Effects of steroids on reintubation and post-extubation stridor in adults: meta-analysis of randomized controlled trials. Critical Care 2009; 13:R49.

3. Lee CH, Peng MJ, Wu CL. Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomized, double-blind, placebo-controlled study. Critical Care. 2007; 11:R72.

4. Bagshaw SM, Farrell C, Drummond J, Brindley PG. Steroids to prevent post-extubation airway obstruction in adult critically ill patients. Can J Anaesth 2008; 55:382-85.

5. Jaber S, Chanques G, Matechki S, Ramonatro M, Vergne C, Souche B, Perrigault PF, Eldjam JJ. Post-extubation stridor in intensive care unit patients. Risk factors evaluation and importance of the cuff leak test. Intensive Care Med 2003; 29:69-74.

6. Francois B, Bellisant E, Gissot V, Dessachy A, Normand S, Boulain T, Brenet O, Preux PM, Vignon P. 12-hour treatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomized double-blind trial. Lancet 2007; 369:1083-89.

7. Darmon JY, Rauss A, Dreyfuss D. et al. Evaluation of risk factors for laryngeal edema after tracheal extubation in adults and its prevention by dexamethasone. A placebo-controlled, double blind, multicentre study. Anaesthesiology 1992;77:245-51.

8. Kriner EJ, Shafazand S, Collice GL. The endotracheal tube cuff-leak test as a predictor for postextubation stridor. Respir Care 2005; 50:1632-8.

9. Fisher MM, Raper RF. The 'cuff-leak' test for extubation. Anaesthesia 1992; 42:10-2.

10. Roberts RJ, Welch SM, Devlin JW. Corticosteroids for prevention of postextubation laryngeal edema in adults. Ann Pharmacother 2008; 42:686-91.

11. TaoFan, Gang Wang, Bing Mao et al. Prophylactic administration of parenteral steroids for preventing airway complication after extubation in adults: meta-analysis of randomized placebo controlled trials. BMJ 2008; 337: a1841.

12. Markovitz BP, Randolph AG. Corticosteroids for the prevention and treatment of postextubation stridor in neonates children and adults.

Cochrane Database Syst Rev 2008; (2): CD-001000.

13. Khemani RG, Randolph A, Markovitz BP. Corticosteroids for the prevention and treatment of postextubation stridor in neonates, children and adults. Cochrane Database Rev 2009; (3):CD001000 (Update of Database Syst Rev 2008; (2):CD001000).

14. Schimmer BP, Parker KL. Adrenocarticotropic hormones, adrenocortical steroids and their synthetic analogues; inhibitous of the synthesis and actions of adrenocortical hormones. In: Goodman and Gilman's: The Pharmacology Basis of Therapeutics. 9th ed. Edited by: Hardman JG, Gilman AG, Limbird LE. New York: McGraw Hill.1996. pp 1459-1486.