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Original Article

Comparison of High- and Low-dose Dexamethasone for Preventing Postextubation Airway Obstruction in Adults: A Prospective, Randomized, Double blind, Placebo-controlled Study☆

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SUMMARY

Background: The study investigated the effectiveness of dexamethasone injections for reducing the occurrence of postextubation airway obstruction (PEAO).
Methods: One hundred and thirty-eight patients who were intubated for ≥ 48 hours with a cuff-leak volume (CLV) < 110 mL were treated with low-dose dexamethasone (5 mg; $n = 41$), high-dose dexamethasone (10 mg; $n = 42$), or placebo (normal saline; $n = 43$) injection every 6 hours for a total of four doses on the day preceding extubation. CLV was measured before the first injection, 1 hour after each injection, and 24 hours after the fourth injection. Extubation was performed 24 hours after the last injection. PEAO was recorded within 48 hours postextubation.
Results: Administration of dexamethasone resulted in a significant increase in absolute CLV and change of CLV relative to baseline tidal volume occurred ($p < 0.05$). However, there was no significant difference between the low- and high-dose dexamethasone groups. The incidence of PEAO was 7.1% in the high-dose group, 9.8% in the low-dose group, and 30.2% in the placebo group. The incidence of PEAO differed significantly between the dexamethasone groups and the placebo group ($p = 0.001$). There was no significant difference in the reintubation rates among the high-dose group (2.1%, 1/42), the low-dose group (2.4%, 1/41), and the placebo group (4.7%, 2/43; $p = 0.79$).
Conclusion: Prophylactic administration of multiple low-dose dexamethasone is sufficient for reducing the incidence of PEAO in high-risk patients.

1. Introduction

Postextubation airway obstruction (PEAO) is a serious complication for intubated patients, which frequently leads to reintubation and a prolongation of intensive care. Previous reports indicated that 2–40% of intensive care unit (ICU) patients develop PEAO requiring reintubation[1,2]. Mortality associated with reintubation has been estimated to be as high as 30–40%[1–4]. Several factors have been correlated with the development of PEAO, including age, female sex, an elevated Acute Physiology Score II, trauma related to endotracheal intubation, excessive tube size, unnecessary tube mobility, increased pressure in cuff, frequent tracheal aspiration, infection, arterial hypotension, and a prolonged period of intubation[5].

Laryngotracheal injury associated with intubation can induce narrowing of the airway due to edema of the glottis, leading to increased risk of PEAO and respiratory distress. The sequelae increased morbidity and mortality[5,6]. The difficulty in establishing a relationship between laryngotracheal edema might be partly due to the presence of an endotracheal tube. In intubated patients, a positive cuff-leak test has been demonstrated to be a predictor of laryngotracheal edema in high-risk patients who could develop PEAO[7–11].

There have been some reports on the effectiveness of corticosteroid therapy prior to extubation for preventing PEAO[12–18]. Most studies employed retrospective analysis of outcomes on subgroups

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of patients who received steroids during their intubation. Moreover, previous studies regarding the efficacy of prophylactic dexamethasone in intubated patients have yielded conflicting results[19–22]. Indeed, the lack of agreement among reports might be attributed to variation in patient age, sex, albumin level, disease severity, setting and duration of endotracheal intubation, dose and duration of treatment, as well as outcome variables and timing of observations, level of sedation, and degree of airway manipulation. Our previous study demonstrated the effectiveness of 5-mg dexamethasone to relieve PEAO[21]. However, we observed no significant difference in the reintubation rate. Therefore we wished to answer two questions; is it possible to prevent laryngeal edema-induced complications by increasing the dosage of dexamethasone therapy? Is cuff-leak volume (CLV) associated with the reintubation rate in high-risk patients?

This study evaluated a subset of high-risk patients who had been intubated for over 48 hours and were undergoing their extubation in an ICU setting. The study objectives were to determine if multiple injections of high-dose dexamethasone were more effective than low-dose dexamethasone to reduce PEAO in patients with a CLV less than 110 mL, and to evaluate whether an after-effect (i.e., transient prevention) persisted following the discontinuation of dexamethasone.

2. Materials and methods

MacKay Memorial Hospital (Taipei, Taiwan) is a tertiary referred hospital. After approval from the Institutional Research Ethics Board, this study was performed in the adult medical ICU. Consecutive patients admitted between 1 April, 2007, and 31 March, 2010, who met the inclusion criteria described below were included in this study. We obtained informed consent from the patients prior to enrollment into the trial. All patients recruited in this study received endotracheal intubation with a high-volume, low-pressure cuffed tube with an internal diameter of 6.5 mm, 7 mm, 7.5 mm, or 8 mm. Patients exhibiting excessive movement were sedated or paralyzed during mechanical ventilation (MV).

All patients were older than 18 years and met all of the following criteria for weaning: (1) pH $\geq$ 7.3; (2) heart rate $\geq$ 70 bpm and $\leq$ 130 bpm; (3) fraction of inspired oxygen (FiO_2) $\leq$ 60%, partial pressure of oxygen (PaO_2) $\geq$ 60 mmHg, and PaO_2/FiO_2 ratio $\geq$ 2 00; (4) rapid and shallow ratio of frequency to tidal volume $\leq$105; (5) temperature $\leq$ 38°C for $\geq$ 8 hours; (6) positive end-expiratory pressure $\leq$ 5 cm H_2O; (7) discontinuous use of sedatives 1 hour before study; (8) minute ventilation $\leq$ 15 L/min; and (9) systolic blood pressure $\geq$ 80 mmHg in the absence of a vasopressor. Supplemental oxygen was continued to maintain an oxygen saturation $\geq$ 95% as measured with a pulse oximeter. Exclusion criteria were either: (1) administration of corticosteroids 7 days prior to extubation; or (2) a history of extubation during the same hospitalization.

Cuff-leak tests were administered to the patients who required MV for > 48 hours and who fit the above criteria. Patients were mechanically ventilated in the volume-assisted control mode using a Bird 8400 STi ventilator (Bird, Palm Springs, CA, USA) with a tidal volume of 10 mL/kg of ideal body weight, a respiratory rate of 20 breaths per minute, and a zero positive end-expiratory pressure during CLV measurement. The balloon cuff was deflated and the expiratory tidal volume was recorded over the next six subsequent respiratory cycles, with the average of the lowest three values used for subsequent analyses. The CLV was determined as the difference in the actual tidal volume before and after cuff deflation.

Patients requiring MV for > 48 hours and exhibiting a CLV $\leq$ 110 mL before planned extubation were included in the trial, as suggested by previous studies[9,10]. A respiratory therapist who was not involved in the patient's care prepared the study drug and the identical-looking placebo. She also recorded all data into a password-protected database. Patients were randomly assigned to receive an intravenous injection of dexamethasone 5 mg, 10 mg, or normal saline at an equivalent volume (placebo) per injection. The medical staff who administered the injections was blinded to the contents of the injections. On the day before extubation, dexamethasone was administered every 6 hours for a total of four doses. We measured CLVs before the first injection, 1 hour after each injection, and 24 hours after the fourth injection. All patients were extubated 24 hours after the last injection of dexamethasone or normal saline.

PEAO (defined as the presence of stridor heard with the aid of a stethoscope) was recorded if it occurred within 48 hours of extubation. The presence of stridor was an indication for the inhalation of racemic epinephrine. Patients experiencing respiratory distress were assigned to receive noninvasive positive-pressure ventilation by face mask if they failed to respond to two doses of epinephrine inhalation and exhibited at least two of the following criteria of respiratory distress: (1) clinical signs suggestive of respiratory-muscle fatigue or increased respiratory effort (the use of accessory muscles, intercostal retraction, or paradoxical motion of the abdomen); (2) hypoxemia (defined as an arterial oxygen saturation < 90% or a PaO_2 < 80 mmHg with an FiO_2 > 50%); (3) a respiratory rate > 25 breaths per minute for 2 consecutive hours; and (4) respiratory acidosis (defined as an arterial pH < 7.35 with a partial pressure of arterial carbon dioxide > 45 mmHg). Patients were reintubated and received MV support if they met at least one of the following criteria: (1) copious secretions that could not be cleared adequately or that were associated with acidosis, hypoxemia, or changes in mental status (somnolence, agitation, or diaphoresis); (2) lack of improvement in signs of respiratory-muscle fatigue; (3) hypotension with an systolic blood pressure < 80 mmHg for > 30 minutes despite adequate volume challenge; (4) a decrease in oxygen saturation to < 85% despite using a high FiO_2 (a PaO_2 < 50 mmHg with an FiO_2 > 70%); (5) a change in mental status rendering the patient unable to tolerate noninvasive ventilation; (6) a diastolic blood pressure drop of > 20 mmHg; or (7) a pH of < 7.3 with a partial pressure of carbon dioxide increase of > 15 mmHg (Figure 1).

Statistical analyses were conducted using the SPSS software package (IBM SPSS Statistics for Windows, version 20.0: IBM Corp., Armonk, NY, USA). We conducted univariate analyses of the dexamethasone and placebo groups using analysis of variance for continuous variables and a Pearson Chi-square test for categorical variables, or Fisher's exact test, as indicated. A p value < 0.05 was considered statistically significant.

3. Results

A total of 588 patients admitted through the ICU received the cuff-leak test during the study period. Four hundred and fifty patients were excluded because of self-extubation (n = 9), deterioration (n = 14), or CLV > 100 mL (n = 427). All of the 138 patients with a CLV less than 110 mL met the inclusion criteria (Figure 2). These patients were randomly assigned to the high-dose (10 mg) dexamethasone group (n = 46), the low-dose (5 mg) dexamethasone group (n = 46), and the placebo group (n = 46). Approximately 91% of the patients (n = 126) in this study successfully completed the course. There were no significant differences in sex, age, weight, height, duration of intubation, diameter of the endotracheal tube, and disease severity among the three groups (Table 1). As shown in Figures 3 and 4, the patients in the dexamethasone groups had a significant increase in absolute CLV and change of CLV relative to baseline tidal volume (percentage; p < 0.05). But there was no