24-hour Pretreatment with Low Dose (0.25mg/Kg/dose) versus High Dose (0.5mg/Kg/dose) Dexamethasone for prevention of Post-Extubation Airway Obstruction in Children: A Randomized Open-label Non-inferiority Trial

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Abstract

Objective: Multi-dose dexamethasone pretreatment prevents postextubation airway obstruction (PEAO), however, its optimal dose in children is not known. We planned to compare effect of 24h pretreatment of low dose (LD) (0.25mg/kg/dose) versus high dose (HD) (0.5mg/kg/dose) dexamethasone for prevention of PEAO. Design: Stratified (for age and intubation duration) randomized open-label non-inferiority trial. Setting: 15-bed Pediatric Intensive Care Unit in a tertiary care teaching hospital of a lower-middle income country. Patients: Children (3mo-12yrs) intubated for [?]48h and planned for first extubation over 26 months (Feb'17 to Mar'19). Children with preexisting upper airway conditions, chronic respiratory diseases, steroid or IVIG therapy in last 7 days, gastrointestinal bleeding, hypertension and hyperglycemia were excluded. Interventions: Low dose (n=144) or high dose (n=143) dexamethasone (q6h) for 6 doses. Extubation was planned after 5th dose. Measurements and Main Results: Patients were monitored for PEAO (Westley's Croup Score >4) for 24 hours. 238 patients were included in per-protocol analysis. 78 patients (33%) developed PEAO; both groups were similar (LD, 41/121, 34% vs HD, 37/117, 32% p=0.71). Risk difference of LD vs HD touches the non-inferiority margin of 0.12 and hence the overall result is non-significant. Incidence of reintubation was also similar (LD, 10/121, 8.3% vs HD, 9/117, 7.7%; p=0.87). Intubation for more than 7 days was an independent risk factor for development of PEAO. Conclusions: Multi-dose 24-hour pretreatment with low dose dexamethasone is not inferior to high dose in preventing PEAO and reintubation among unselected patients in the studied clinical setting. Multi-centric trials with larger sample size among children at high risk of developing PEAO are needed.

INTRODUCTION

Postextubation airway obstruction (PEAO) is common in pediatric intensive care units (PICUs) [1-4] and have potential for re-intubation [1,4,5]. Reintubation increases morbidity, mortality and cost of care. Incidence is higher in low-resource settings, as children get intubated in emergency and uncontrolled situations, have multiple airway manipulations and hypoalbuminemic edema at the time of extubation [1]. Multi-dose pre-treatment with systemic steroids seems to prevent PEAO in at-risk adults [6-10], as well as in children[1,5,9]. We demonstrated reduction in incidence (82% vs 65%) and severity of PEAO with 24h pretreatment with multi-dose dexamethasone (0.5 mg/Kg/dose; max, 8 mg/dose; q6h; total of 6 doses) compared to 6h pre-treatment in a clinical setting with high incidence of PEAO [1]. Though dexamethasone at this dose was safe in small studies [1,11], there is a potential for hypertension, upper gastrointestinal bleeding, hyperglycemia, glycosuria and sepsis [11,12]. Hypertension is likely to add to the autonomic instability observed during iatrogenic withdrawal syndrome. Suggested dose of dexamethasone for children varies widely from 0.25 mg/Kg/dose to 0.50

mg/Kg/dose [12]. Some centers even use a dose of 0.15 mg/Kg/dose, while many other centers do not use dexamethasone at all. There is felt need for more evidence to identify the prophylactic role of dexamethasone [9] and to define its optimal dose in children [12].

Recently, low dose dexamethasone pretreatment (5 mg/dose, q6h, total of 4 doses) was shown to be equally effective as the high dose (10 mg/dose, q6h, total of 4 doses) in preventing PEAO among at-risk adult patients from Taiwan [8]. Inspired by these results and lack of information on optimal dose in children, we conducted this trial to assess the effectiveness of half of the currently used dose in our unit (i.e., 0.25 mg/Kg/dose; maximum, 4 mg/dose; q6h; total of 6 doses) in preventing PEAO. It was a non-funded time-bound dissertation project as part of the 3-year fellowship program in Pediatric Critical Care, and was registered with Clinical Trials Registry-India vide registration number CTRI/2017/08/009273.

Materials and Methods

Study Participants

Study was performed in a 15-bed PICU over a period of 26 months (February 2017 to March 2019) in a lower-middle income country. PICU is part of a 1740 multi-specialty tertiary care teaching hospital (annual admission, ˜ 23,000), and admits ˜ 950 and ventilates ˜ 400 patients per year. Parents or legal guardians gave written informed consent before enrollment into the study. Eligibility criteria included age >3 months and < 12 years, intubation for > 48h, and anticipated to have their first planned extubation during next 24h as in our previous study[1]. Patients with actual or potential poor airway reflexes, Glasgow Coma Score (GCS) < 8, pre-existing airway issues, previous tracheal intubation or tracheostomy, chronic lung disease, contraindications for steroid, gastrointestinal bleeding, hypertension (>95th centile), hyperglycemia, steroid or chronic NSAID therapy were excluded. Patients were also excluded if their extubation was deferred or they got self-extubated.

Randomization, intervention, and data collection

Assignment of treatment [low dose (LD), 0.25mg/Kg/dose dexamethasone, max 4mg/Kg/dose; OR high dose (HD), 0.5mg/Kg/dose dexamethasone, max 8mg/Kg/dose] in the eligible patients was done by stratified block randomization using variable block sizes of four to eight. Random allocation sequence was generated by web-based program by an individual not involved in study. Patients were stratified according to age (<1 years, 1 to <5 years, and > 5 years) and duration of intubation ([?]72 hours, >72 hours but< 7 days, and >7 days). Opaque sealed envelopes containing interventional doses of dexamethasone for two assignments were serially numbered on the outside. We could not achieve the blinding as we used two different doses of a commercially available drug preparation. However, none of the investigators were directly involved in the monitoring and clinical decisions during post-extubation period.

Control patients (HD patients) were planned to receive a total of six doses of intravenous dexamethasone (0.5mg/kg/dose, max 8mg/dose), first dose 24 hours before anticipated extubation and then every 6 hours for a total of six doses as per the current practice in the unit. Study patients (LD patients) were planned to receive six doses of intravenous dexamethasone (0.25 mg/Kg/dose, max 4mg/dose) similarly. The extubation was planned during daytime immediately after the 5thdose of dexamethasone. Study protocol was approved by Institute Ethics Committee, Institute Thesis Committee and Departmental Review Board.

Intubation, Care of intubated patients, Extubation and Outcome Parameters

Baseline clinical characteristics were recorded as per our previous trial [1]. Patients were intubated by oro-tracheal route in Pediatric Emergency Room, Children wards or PICU by the on-duty Pediatric Junior Resident, Pediatric Senior Resident or Pediatric Critical Care Fellow. Care of intubated patients, elective extubation, post-extubation monitoring and management was done as per our published protocol [. Patient ventilated on Hamilton G-5® ventilator during the study period. Over the last few years, we established a protocol to actively manage fluid overload with continuous furosemide infusion (0.05-0.1 mg/Kg/h) after hemodynamic stabilization, especially prior to extubation. Sometimes, children received albumin as well to get rid of fluid overload. Duration and intensity of diuresis, and optimization of fluid de-resuscitation were

decided by the treating team. Peritubal leak was not considered while taking decision for extubation. Patients were monitored for 24 hours post-extubation for development of PEAO [defined as a Westley's Croup Score (WCS) of > 4][13] and/or need for reintubation due to PEAO (WCS$>$ 7). Presence of PEAO based on WCS and need for re-intubation for PEAO were assessed by minimum of two clinicians (one pediatric Junior Resident and one Pediatric Critical Care Fellow), which was then managed with adrenaline nebulization and/or re-intubation. Treatment safety was assessed for occurrence of upper gastrointestinal bleeding, hyperglycemia, hypertension and infection for 5 days after last dose of dexamethasone. Dexamethasone was discontinued if any contraindication developed during the study, and patient was excluded. The outcome parameters evaluated were as in our previous trial[1]

Statistical analysis

PEAO was defined as WCS > 4. Post-extubation, patients were treated with adrenaline nebulization if WCS was$>$ 4, and reintubated if so required. We wanted to make sure that 95% confidence interval (CI) of the low dose arm does not overlap with 95% CI of the previously described placebo arm of a trial which was done in a setting similar to ours. In a previous small placebo-controlled trial [11], incidence of PEAO sufficient to require adrenaline nebulization was 69% (22/32; exact binomial 95% CI, 50-83.9%) in placebo group compared to 13% (4/31; exact binomial 95% CI, 3.6-29.8%) in the HD arm (0.5mg/Kg/dose). If we arbitrarily assume an incidence of 15% in the LD arm with a non-inferiority margin of 12% from the baseline incidence of HD arm, a sample size of 478 patients (239 in each treatment arm) would be required to prove non-inferiority of LD (0.25mg/Kg/dose) treatment regime over the HD (0.5mg/Kg/dose) treatment regime with 80% power and 5% one-sided α-error. Considering attrition of 10%, 526 patients would be required (263 patients in each treatment arm).

Per-protocol analysis was performed with SPSS version 22 (IBM®). Patients with self-extubation, deferred extubation and those who were reintubated due to non-PEAO reasons were*a priori* deemed un-assessable and were excluded from analysis. Continuous and categorical variables were analyzed by Mann-Whitney U test and Chi-square test (and Fisher exact test if needed) respectively. Relative risk (RR) and their 95% confidence interval (CI) were estimated for the primary endpoint. Two-way mixed model ANOVA was used for intergroup comparisons of Westley's Croup Score during 24 hours post-extubation. Time to recovery from PEAO (i.e., time to achieve WCS$<$ 2 irreversibly) was compared by Kaplan-Meier Curve after censoring those who could not achieve WCS$<$ 2 during 24 hours of observation. To identify independent risk factors for PEAO and changes over last decade, *post hoc* univariate analysis followed by multivariate analysis were performed. Multivariate analysis was done with ENTER selection procedure incorporating variables with p-value of <0.05 in univariate analysis. A p-value of <0.05 indicated significance.

Results:

Figure 1 shows the study flowchart. Out of 768 patients intubated during the study period, 287 patients were enrolled and randomized into two groups. Some patients (n=36) were missed despite best efforts of the trainee fellow (BP) due to his other commitments. Table 1 shows admitting diagnosis and indication for PICU admission, while Table 2 shows baseline characteristics. Extubation was deferred in 21 patients for various reasons [neurogenic breathing (5), persistent encephalopathy (5), central apnea (3), neuromuscular weakness (2), seizures (2), pulmonary hemorrhage (1), pulmonary arterial hypertension (1), intracranial bleeding (1) and lung collapse (1)]. Twenty-eight patients (14 in each group) needed reintubation for non-PEAO reasons [persistent encephalopathy (9), neurogenic breathing (6), pulmonary hemorrhage (4), poor respiratory efforts (4), lung collapse (2), generalized spasms (1), seizures (1) and central apnea (1)]. After excluding these, 238 patients were available for per-protocol analysis (Figure 1). More than one-third of patients (36%) had chronic malnutrition, while 41% had acute malnutrition. Median body mass index was ˜15Kg/m^2. Respiratory failure (50%) was the commonest indication for PICU admission, followed by intracranial hypertension (22%). Baseline characteristics of the enrolled cohort (n=287) were similar to the assessable one (n=238) (data not shown). Among assessable patients (n=238), median duration of intubation and/or hand ventilation in pre-PICU areas was 12h (IQR, 0-24). Sixty-four (27%) patients spent $>$ 24 h in emergency room or pediatric wards before they could get transferred to PICU. Fourty-two (18%) children had multiple airway

manipulations (i.e., had to be reintubated for accidental extubation or tube obstruction) before their first elective extubation; 10 patients were reintubated for more than once. It is not that rare in our setting due to inadequate nursing care. As treating team was given liberty to time extubation based on the prevalent clinical situation, patients received a median of four dexamethasone doses prior to extubation instead of the planned five; 36 (15%) patients received three doses or less. Serum albumin levels were not available in 22 patients at extubation. Hypoalbuminemia and clinically manifest edema were present in 75% (162/216) and 26% of patients respectively. Both groups were comparable at baseline.

A total of 78 patients (33%) developed PEAO with no difference between two groups [LD, 41/121 (risk ratio, 0.34) vs HD, 37/117 (risk ratio, 0.32); p=0.71] (Table 3). The risk difference between the LD and HD group is 0.02 (90% CI, -0.07 to 0.12). The confidence interval of risk difference touches the non-inferiority margin of 0.12, hence the overall result is non-significant. Nineteen patients (19/238, 8%) needed reintubation with similar incidence in two groups [LD, 10/121 (8%) vs HD, 9/117 (7.8%); p=0.87]. Among PEAO patients (WCS[?]4) not requiring reintubation (n=59; LD, 31 vs HD, 28), mean WCS was similar at different points of post-extubation observation (two-way mixed model ANOVA, interactional p=0.22) [Figure 2 (A)]. Further, there was no difference in time to recovery from PEAO (i.e., time to achieve WCS< 2 irreversibly) between two groups (log-rank test, p=0.90) [Figure 2 (B)]. Even after including 28 patients who were clinically considered to be re-intubated due to non-PEAO reasons (14 in each group), no difference was observed in incidence of either PEAO [LD, 55/135 (41%) vs HD, 51/131 (39%); p=0.76] or reintubation [LD, 24/135 (18%) vs HD, 23/131 (18%); p=0.96].

Post hoc analysis revealed non-significant increase in occurrence of PEAO in the subgroup of children intubated for more than 7 days (n=91) with the low dose regime [LD, 25/46 (54%) vs HD, 16/45 (36%); RR, 1.52; 95%CI, 0.95-2.45; p=0.07]. However, incidence of reintubation was comparable among children intubated for more than 7 days with the two dose regimes [LD, 6/46 (13%) vs HD, 5/45 (11%); p=0.77].

Univariate analysis identified longer (>7 days) intubation, prolong ventilation and higher PRISM III score as significant risk factors for PEAO (Table 3). Multiple airway manipulations prior to the first elective extubation seems to be another risk factor for PEAO (p=0.058; RR, 0.67; 95% CI, 0.45-0.99). Dexamethasone dose (0.25 vs 0.5 mg/Kg/dose) or whether patients received three or more doses prior to extubation did not affect occurrence of PEAO. Model for multivariate analysis included higher PRISM III score, longer (>7 days) intubation and duration of assisted ventilation. The latter two were proven to be independent risk factors for development of PEAO in the studied cohort (Table 3). Also, children intubated for more than 7 days had twice the chance of getting reintubated for PEAO compared to those who had shorter intubation [>7 days, 11/91 (12%) vs< 7 days, 8/147 (5.4%); RR, 2.22; 95%CI, 0.93-5.31; p-value, 0.07].

One patient with expanded dengue syndrome (with thrombocytopenia and coagulopathy) succumbed to a bout of massive hematemesis after 3 days of the last dexamethasone dose. None developed hypertension, hyperglycemia, signs infection or any other event attributable to dexamethasone during 5 days of follow up.

Discussion

Multi-dose pretreatment regime of systemic steroid starting 12-24 hours prior to planned extubation reduces PEAO in adult [6-10]as well as in pediatric [1,9] patients. Dexamethasone is preferred over other steroids [1,7,8]. Our previous study (period: 2009-10) demonstrated that 24-hour pretreatment with a high dose of dexamethasone prevents PEAO and need of reintubation[1]. Majority of the then patient population in our unit had multiple risk factors e.g., intubation in uncontrolled situations, longer duration of intubation and hand ventilation in emergency room, multiple airway manipulations and hypoalbuminemic edema. Inspired by the findings of non-superiority of the high dose (versus the low dose) in the adult patients [8] and lack of similar information in the pediatric literature, we conducted the present trial (period: 2017-19). It has not only shown the non-inferiority of the low dose (0.25mg/Kg/dose) pretreatment (versus previously studied high dose, 0.5mg/Kg/dose) in reducing PEAO, but it also demonstrated the changing clinical scenario in the unit during the last decade.

Comparison of clinical characteristics and potential risk factors for PEAO during these two study periods

is given in the supplemental table 1. While our patients continue to be similarly malnourished, PRISM III score has increased. Now, we saw more patients with presumptive diagnosis of CNS infections (e.g., meningitis, meningoencephalitis), while patients with respiratory infections (e.g., pneumonia, empyema) has decreased. Frequency of risk factors, as identified in the previous trial (2009-10), were much lesser during the current study period (2017-19). Number of patients intubated in uncontrolled situations (89% vs 76%) got reduced as was duration of intubation and/or hand-ventilation in pre-PICU areas (PER/wards) (median, 0.9 days vs 12 hours). Number of patients needed to stay in PER/wards for$>$ 24 hours prior to PICU transfer (57% vs 27%) and undergoing multiple airway manipulations (35% vs 18%) got reduced by half. Number of patients with $>$7 days of intubation and/or ventilation also got reduced by a third (56% vs 38%). Serum albumin was higher (median, 2.5 gm/dL vs 2.8 gm/dL) at the time of extubation, while lesser number of patients had hypoalbuminemia (88% vs 75%) and clinical edema (40% vs 27%). All these led to a notable reduction in PEAO (73% vs 33%) during the current study period despite using the same yardstick (i.e., WCS). Reintubation rate remained unchanged over last 10 years (11% vs 8%). Incidence of PEAO and reintubation in our unit seems to be approaching towards what is being reported from PICUs of high-income countries [2,5,14]. The two study cohorts, a decade apart, provide a glimpse of journey of a PICU in a tertiary care teaching hospital in a lower-middle-income country.

We could not find any new pediatric trial since we published results of our previous study. Recently, effectiveness of dexamethasone pretreatment in reducing reintubation due to PEAO was reported in a retrospective propensity matched study on infants with respiratory syncytial virus [5]. A systematic review and meta-analysis of 11 adult trials [10] proved efficacy of steroid pretreatment in prevention of PEAO and reintubation in select group of at-risk patients. A randomized control trial among at-risk adult patients (cuff-leak volume $<$110ml) revealed effectiveness of dexamethasone pretreatment in reducing PEAO (placebo group, 30% vs two dexamethasone groups, 9.8% and 7.1% respectively). However, there was no difference between the low dose (5 mg/dose) and the high dose (10 mg/dose) regimes [8] similar to the findings observed in the current study. Low dose dexamethasone reduced the baseline incidence of PEAO from 30% (in the placebo arm) to 9.8%, and further reduction could not be achieved with the higher dose. Similarly, lack of difference in the two dose regimes may be attributable to the significantly reduced incidence of PEAO itself (73% vs 33%), with notable weakening of the associated high-risk factors. However, it is not sure if these findings would be replicable in a clinical setting similar to what we had a decade ago, i.e., very high incidence of PEAO with presence of multiple risk factors in the majority. The study reiterates the situation-specific applicability of the evidence generated from various clinical settings[15].

Dexamethasone pretreatment is found to be effective only among at-risk adult patients, and not among unselected ones [10]. We also demonstrated a lesser incidence of PEAO with high dose dexamethasone pretreatment in the subgroup of children intubated for more than 7 days [RR, 1.52; p-value, 0.07]. Trials to assess effectiveness of various dexamethasone pretreatment regimes in the select group of high-risk children are advisable in context of reducing incidence of PEAO and plateauing of reintubation in the studied clinical setting. Indices based on pre-extubation airway ultrasound[16-19] may help identify high-risk children.

Based on the assumptions used for sample size calculation in 'Material & Methods' section, the power of the study is less than 60%. With demonstrated PEAO incidence of 32% and 34% in HD and LD arms respectively in our study, with non-inferiority margin of 12%, one sided α-error of 0.05 and power of 80%, a sample size of 398 per group (796 in total) would be required to prove the non-inferiority of LD compared to HD. With the new assumptions also, the power of study is less than 60%. The study was a non-funded time-bound dissertation project. Due to logistics and time-constraints, we could enroll only 238 patients. Two categories of exclusions may raise concerns of bias— patients with deferred extubation (n=21) and patients who were reintubated for non-PEAO reasons (n=28). Inclusion of the former would be unfair as they were not available for assessment of treatment effect. Results after including those reintubated for non-PEAO reasons (n=28) was no different. Relying on clinical scores to identify and monitor PEAO lacks objectivity; respiratory inductance plethysmography and esophageal manometry (which is not available with us) would have been better [14]. Lack of measurement of observer agreement[2] and blinding are other concerns. To limit the former, minimum of two clinicians assessed the patients for PEAO and/or need for reintubation.

The latter could not have been addressed as dexamethasone doses were drawn from the same commercially available preparation, and we do not have in-house pharmacy. A placebo arm in the trial would have demonstrated the role of dexamethasone pretreatment better, however it would be unethical when our unit's standard of care includes dexamethasone pretreatment for children intubated for> 48 hours. Since it is a single-center study, external validity may be a concern. Enrolment over a short period of 26 months indicates contemporary nature of the cohort. Stratification of randomization using intubation duration is a strength. Despite many limitations, the trial provides clinically relevant data to the pediatric critical care community working in low- and middle-income countries (LMICs) and experiencing high incidence of PEAO as ours.

Conclusions

Incidence of PEAO has got significantly reduced in our unit during the last decade. Though the study was not powered enough, it showed non-inferiority of multi-dose 24h pretreatment with the low dose (0.25mg/kg/dose) dexamethasone compared to the high dose (0.5mg/kg/dose) regime in preventing PEAO and reintubation in the studied clinical setting. Intubation for more than 7 days continues to be an independent risk factor, where high dose seems to show a beneficial trend. Multicentric trials involving PICUs from LMICs experiencing high incidence of PEAO with larger sample size among children at high risk are needed.

REFERENCES

1. Baranwal AK, Meena JP, Singhi SC, Muralidharan J. Dexamethasone pretreatment for 24h versus 6h for prevention of postextubation airway obstruction in children: a randomized double-blind trial. Intensive Care Med. 2014; 40:1285–94.
2. Khemani RG, Schneider JB, Morzov R, Markovitz B, Newth CJ. Pediatric upper airway obstruction: interobserver variability is the road to perdition. J Crit Care. 2013; 28: 490-7.
3. Nascimento MS, Prado C, Troster EJ, Valério N, Alith MB, Almeida JF. Risk factors for post-extubation stridor in children: the role of orotracheal cannula. Einstein (Sao Paulo). 2015; 13: 226-31.
4. Sinha A, Jayashree M, Singhi S. Aerosolized L-epinephrine vs budesonide for post-extubation stridor: A randomized controlled trial. Indian Pediatr. 2010; 47: 317-22.
5. Veldhoen ES, Smulders CA, Kappen TH, Calis JC, van Woensel J, Raymakers-Janssen PAM, Bont LJ, Hennus MP. Post-extubation stridor in Respiratory Syncytial Virus bronchiolitis: Is there a role for prophylactic dexamethasone? PLoS One. 2017; 12: e0172096.
6. François B, Bellissant E, Gissot V, Desachy A, Normand S, Boulain T, et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial. Lancet. 2007; 369: 1083–9.
7. Lee C-H, Peng M-J, Wu C-L. Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomized, double-blind, placebo-controlled study. Crit Care. 2007; 11: R72.
8. Lin C-Y, Cheng K-H, Kou L-K, Lee C-H. Comparison of High- and Low-dose Dexamethasone for Preventing Postextubation Airway Obstruction in Adults: A Prospective, Randomized, Double blind, Placebo-controlled Study. Int J Gerontol. 2016; 10: 11–6.
9. Khemani RG, Randolph A, Markovitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. Cochrane Database Syst Rev. 2009 Jul 8;3:CD001000.
10. Kuriyama A, Umakoshi N, Sun R. Prophylactic Corticosteroids for Prevention of Postextubation Stridor and Reintubation in Adults: A Systematic Review and Meta-analysis. Chest. 2017; 151: 1002-1010.
11. Anene O, Meert KL, Uy H, Simpson P, Sarnaik AP. Dexamethasone for the prevention of postextubation airway obstruction: a prospective, randomized, double-blind, placebo-controlled trial. Crit Care Med. 1996; 24: 1666-1669.
12. McCaffrey J, Farrell C, Whiting P, et al. Corticosteroids to prevent extubation failure: a systematic review and meta-analysis. Intensive Care Medicine. 2009; 35: 977–986.
13. Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup: a double-blind study. Am J Dis Child 1978; 132: 484–7.

14. Khemani RG, Hotz J, Morzov R, Flink R, Kamerkar A, Ross PA, Newth CJ. Evaluating Risk Factors for Pediatric Post-extubation Upper Airway Obstruction Using a Physiology-based Tool. Am J Respir Crit Care Med. 2016; 193: 198-209.
15. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. 2010 Dec 30. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53480/ [Accessed on Nov 6, 2019]
16. Ding LW, Wang HC, Wu HD, et al. Laryngeal ultrasound: a useful method in predicting post-extubation stridor. A pilot study. Eur Respir J. 2006; 27:384-389.
17. Sutherasan Y, Theerawit P, Hongphanut T, et al. Predicting laryngeal edema in intubated patients by portable intensive care unit ultrasound. J Crit Care. 2013; 28: 675-680.
18. El Amrousy D, Elkashlan M, Elshmaa N, et al. Ultrasound-Guided Laryngeal Air Column Width Difference as a New Predictor for Postextubation Stridor in Children. Crit Care Med. 2018;46:e496-e501.
19. Madhusudan S. Feasibility study of clinician-performed ultrasonographic assessment of airway of intubated children to predict postextubation airway obstruction. Dissertation submitted for DM (Pediatric Critical Care) to Postgraduate Institute of Medical Education & Research, Chandigarh (India). December, 2017.
20. Horowitz IN, Tai K. Hypoalbuminemia in critically ill children. Arch Pediatr Adolesc Med. 2007; 161: 1048–52.

LEGEND for FIGURES

Figure 1 : Study Flowchart

Figure 2: (A) Line diagram comparing the WCS (mean +SEM) in non-reintubated patients of the two groups during post-extubation observation period (interactional p=0.22). **(B)**Kaplan Meier Curve for time to irreversibly achieve WCS< 2 during postextubation observation period (Log rank test, p=0.90).

ROLE OF CONTRIBUTORS

AKB conceptualized, planned and developed the study design, oversaw the conduct of the study and statistical analysis, prepared the final draft of the manuscript and will act as guarantor. BP enrolled patients, executed the study protocol, did literature search, statistical analysis and prepared the first draft of the manuscript. PKM guided the statistical analysis. JM critically reviewed and approved the manuscript.

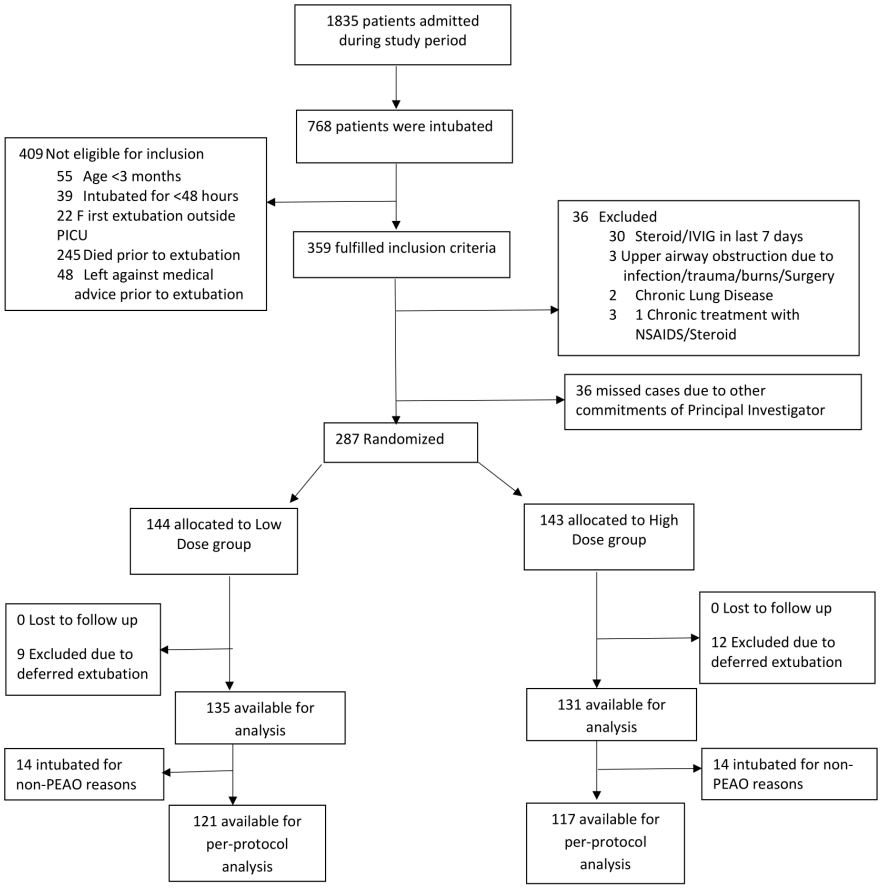
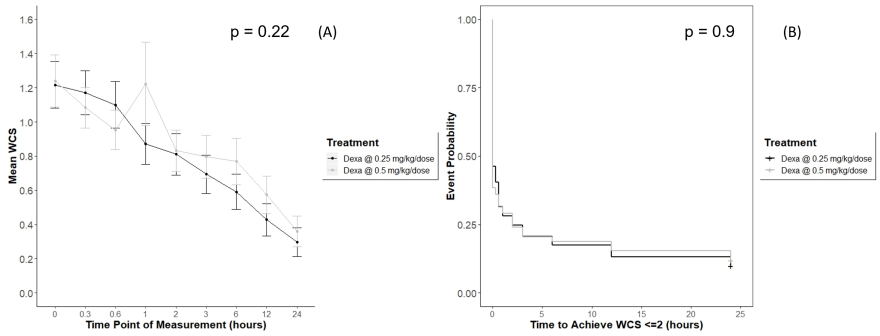


Figure 1: Study Flowchart



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