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The use of prophylactic corticosteroids to reduce post-extubation stridor in pediatric patients: a systematic review

M. Dekeyser (*), J. Gunst (**), V. De Sloovere (*)

Abstract: The incidence of extubation failure ranges from 4 to 68,75% in pediatric population in the intensive care unit (ICU). Extubation failure and the need for reintubation are correlated with increased morbidity, mortality and higher costs. Multiple studies investigated the efficacy of corticosteroids (CS) to prevent post-extubation stridor (PES), mainly in adults. Due to the differences in laryngeal anatomy between children and adults, children may be more prone to PES. There is still no consensus about the prophylactic use of CS for PES in children. We conducted a systematic review to collect the evidence.

We searched three different databases: MEDLINE, EMBASE and Cochrane library. The following terms: "pediatric", "extubation", "laryngeal edema" and "corticosteroids" were searched in title and abstract.

1097 references were collected and 201 references met the criteria for full text review. Finally, nine randomized controlled trials (RCT's) were included, enrolling 23 to 153 patients. There was a considerable heterogeneity in design, and all studies had a moderate to high risk of bias. Five RCT's showed a significantly lower incidence of PES or extubation failure by CS treatment. Reported adverse effects of CS were low. We conclude that CS may be effective and safe to reduce post-extubation stridor in children, although the level of evidence is low.

Keywords: steroids; airway extubation; laryngeal edema; pediatric.

Introduction

Mechanical ventilation is a lifesaving treatment in respiratory failure and is facilitated by endotracheal intubation. Recently, non-invasive ventilatory techniques are more routinely used to avoid endotracheal intubation such as high flow nasal cannula oxygen (HFNCO2), continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) (1). Despite these techniques, endotracheal intubation remains the most frequently used and safest way to protect the airway, but this is not without risks or side effects. Certainly in pediatric patients, where the laryngeal anatomy differs from adults. In these patients, the narrowest point of the larynx is not at the level of the vocal cords but at the cricoid cartilage, the laryngeal cartilage is more floppy and the airways are smaller and therefore more rapidly compromised (2). An endotracheal tube (ETT) can cause laryngeal or tracheal trauma, due to the pressure on the mucosa of the airway or by multiple manipulations of the ETT. Laryngeal edema (LE) and tracheal stenosis can occur (3). Post-extubation LE can lead to upper airway obstruction, extubation failure and in some cases reintubation will be necessary (4). The incidence of extubation failure ranges from 4 to 68,75% in pediatric population in the intensive care unit (ICU) (5, 6, 7, 8). Other reasons for extubation failure are respiratory muscle weakness, pulmonary dysfunction, neurologic impairment or residual effect of muscle relaxants and/or sedatives (6). Extubation failure and the need for reintubation are correlated with increased morbidity, mortality and higher costs (9, 10, 11). Hence, prevention of post-extubation stridor (PES) and extubation failure is important.

Multiple studies investigated the efficacy of corticosteroids (CS) to prevent PES, mainly in adults. Due to the earlier mentioned differences in laryngeal anatomy between children and adults, children may be particularly vulnerable to PES. However, there is no consensus about the prophylactic use of CS in children. CS are hypothesized to prevent LE and as a result PES. Glucocorticoid therapy inhibits inflammatory mediators and promotes

M. Dekeyser, MD; J. Gunst, MD, PhD; V. De Sloovere, MD.
(*) Department of anesthesiology, University Hospital of Leuven, 3000 Leuven, Belgium.
(**) Department of intensive care medicine, University Hospital of Leuven, 3000 Leuven, Belgium.
Corresponding author: Dekeyser M, University Hospital of Leuven, Department of anesthesiology; Herestraat 49, 3000 Leuven, Belgium.
Email: dekeyser.melanie@gmail.com

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vasoconstriction as well (8). Several animal studies demonstrated the anti-inflammatory effect of CS on airway trauma (12, 13). CS are frequently used as anti-inflammatory drug, despite the fact that they can cause serious side effects, like gastro-intestinal bleeding, hyperglycemia, arterial hypertension and infections.

In this systematic review, we investigated the efficacy and safety of prophylactic CS therapy to prevent PES in pediatric patients (0-12years old).

Methods

We used the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement and the 24-step guide of Muka et al. to construct our research (14). The search was based on the PICO model. Patient population included intubated infants (birth till 1year old) or children (till 12years old) mechanically ventilated in the operating room (OR) or the pediatric intensive care unit (PICU). Concerning the intervention, we investigated the prophylactic use of CS (including different administration methods: intramuscular (IM), intravenous (IV) or by inhalation). The control group should have received no drug or placebo. We analyzed the effect of CS to prevent PES as primary outcome. The secondary outcomes are the presence of an upper airway obstruction (UAO), the need for epinephrine aerosol post-extubation and the need for reintubation. Inclusion and exclusion criteria were defined before we ran the search (Table 1). We only included RCT's, written in English or Dutch.

Table 1

Study design with inclusion and exclusion criteria

The use of corticosteroids to reduce post-extubation stridor in children
Study Design: Randomized controlled trial
Exposures: Intubated children in OR or PICU **Treatment intervention**: prophylactic corticosteroids before extubation (scheme)
Outcomes: Upper laryngeal obstruction post-extubation/post-extubation stridor
Inclusion criteria: 1. Studies in children from 0-12years old 2. Studies reporting post-extubation stridor or upper laryngeal obstruction or reintubation 3. English or Dutch written
Exclusion criteria: – Studies in animals – Articles with incomplete information – Systematic review and meta-analysis – Meeting/congress reports – Non-randomized controlled study

One of the outcome parameters in the studies should be post-extubation stridor, upper airway obstruction or reintubation.

We searched three different databases: MEDLINE, EMBASE and Cochrane library. The following terms: "pediatric", "extubation", "laryngeal edema" and "corticosteroids" were searched in title and abstract, taking into account all possible synonyms. The full search strategy is included in Appendix 1. We collected all references in the online software Rayyan. This software provides duplicate clearance and tracking of reason for exclusion. The title and abstracts were screened by MD for inclusion and exclusion criteria as mentioned before (Table 1). Of the eligible references, full text was retrieved. We also conducted a forward search. The detailed data of the included articles were collected in an Excel format. All RCT's were assessed for risk of bias using the second version of the Cochrane risk-of-bias tool for randomized trials (RoB2) (15).

Results

The search was conducted on the 12th of July 2020, the databases were searched from the beginning of registration till the search date. From MEDLINE (January 1963 till July 2020), EMBASE (January 1973 till July 2020) and Cochrane Library (January 1987 till July 2020), we retrieved 1097 references, after duplicates were removed. References were screened, when both title and abstract were available. When there was no abstract, the references were included in the full text review. 201 references met the criteria for full text review. If available, we screened the full text according to the predefined inclusion and exclusion criteria. No extra articles were retained from the forward search. 192 articles were excluded: numbers and reason for exclusion are found in the flow diagram (Fig. 1). Finally, nine RCT's were included. The individual study's characteristics are summarized in Table 2.

Patient characteristics

In total, the nine included papers investigated 692 patients, ranging from 23 to 153 participants per study. The age ranges from 0-18 years. Couser et al. only investigated infants under the age of two months: high risk preterm infants with low birth weight (16). The three most recent studies did not include neonates under 1 month of age (17-19). Tellez et al. did not specify the upper limit of the age range (20).

All included patients were extubated in a PICU

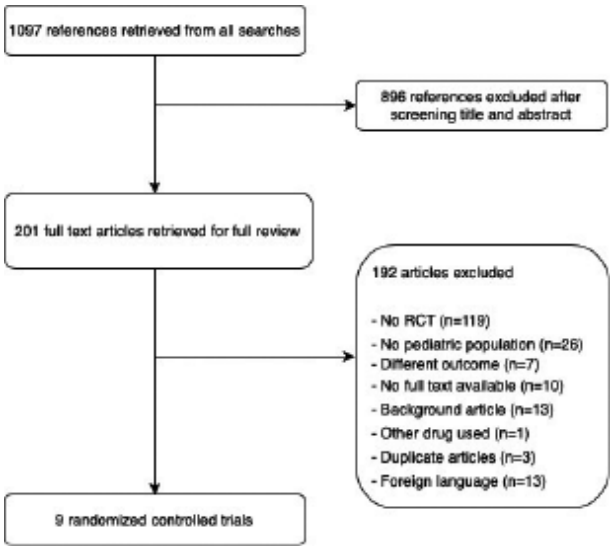

Fig. 1. — Flow diagram screened, assessed and included studies (N= number of articles).

setting. The location and/or the physician who intubated the patients differed among the studies: some were intubated in the PICU, others externally (in another hospital prior to transfer), some in the emergency room while others were intubated for elective surgery in the OR.

Inclusion and exclusion criteria differ between the included studies. Harel et al. exclusively included patients with previously failed extubation (21). High risk patients with multiple intubations were only found eligible in four studies (8, 19-21). In five out of nine studies, patients with airway abnormalities or trauma were excluded (8, 17, 19, 20, 22) Anene et al. included patients with airway abnormalities, but excluded children with laryngotracheal infections (23).

Corticosteroid scheme

All studies except one, administered CS intravenously (dexamethasone or methylprednisolone) before extubation, Prasertsan et al. investigated the effectiveness of nebulized fluticasone administered just after extubation versus placebo aerosols (19). Drago et al. is the only group that studied methylprednisolone with a loading dose, continuous infusion and tapering (18). The other articles studied dexamethasone in a dosage from 0,2mg/kg/dose to 0,5mg/kg/dose every 4 to 6 hours during a variable period of time, with the start of intervention ranging from 1 hour to 24 hours prior to extubation (Table 2).

Outcome

In the included RCT's, the severity of PES is scored differently. Some studies used Westley's Croup Score (WCS), with different cut offs to start treatment with nebulized epinephrine or reintubation (8, 17, 19). The WCS is a commonly cited croup severity score, mainly used for research purposes. The extremely high incidence of PES in the study of Cesar et al. was probably due to the cutoff of WCS more than zero, where other studies use a cutoff of two or four (8).

Three papers showed a significant reduction of PES in the CS group. A statistical significant reduction in stridor and significantly better dynamic compliance was seen in the CS group of Couser et al (16). In the study of Malhotra, the occurrence of laryngeal edema was significantly higher in the pediatric control group (63.33%) compared to the pediatric dexamethasone group (26.67%) (22). Baranwal et al. reported a significant reduction of PES with a 24-hour pretreatment of CS versus a 6-hour pretreatment (17).

Four included articles did not find a significant difference between the CS group and the placebo group with regard to PES. Tellez et al. prematurely stopped recruiting due to no significant difference in PES [RR=0,63 (CI 95% 0,3-1,31)] in 153 participants after preliminary analysis. The authors claimed enlarging sample size would be neither practical nor ethical (20). Harel et al. found no statistical significant difference of stridor score between groups, although the stridor score was related to the success of extubation. They found that failure of extubation associated with neurological impairment. The majority of the included patients, sixteen of 23 patients (69,5%), were diagnosed with neurological impairment, either acute or chronic or both. Acute impairment included acute central nerve system (CNS) injury, other patients had a history of developmental impairment (21). The four study groups of Cesar et al. showed no significant difference. Their overall incidence of PES was very high (68,75%) (8). The only study with inhalation CS by Prasertsan et al., found no significant difference for PES with prophylactic nebulized fluticasone (19).

Other studied outcome parameters are the need for administration of epinephrine aerosols and the need for reintubation due to UAO. In the study of Anene et al., they found a lower frequency of stridor and croup score without statistical significance, but the need for epinephrine aerosols was significantly reduced, as was the need for reintubation (23).

Table 2

Summary of included articles

	Author	Year of publication	Country	Type of study	Statistical analysis	#participants	Age
l-Epinephrine and dexamethasone in postextubation airway obstruc-tion: A prospective, randomized, double-blind placebo-controlled study	Cesar	2009	Brazil	Prospective, randomized, double-blinded placebo-controlled	Chi square, ANOVA	64	1d-12y
Dexamethasone pretreatment for 24 h versus 6 h for prevention of postextubation airway obstruction in children: a randomized double-blind trial	Baranwal	2014	India	randomized, placebo-controlled, double-blind trial	Mann–Whitney U, Chi square, Fisher exact, ANOVA	124	3m-12y
Double-Blind, Placebo-Controlled Pilot Randomized Trial of Methylprednisolone Infusion in Pediatric Acute Respiratory Distress Syndrome	Drago	2015	USA	Double-Blind, Placebo-Controlled Pilot Randomized Trial	Student t or Mann-Whitney U; Analysis of variance (ANOVA)	35	1m-18y
Dexamethasone for the prevention of postextubation airway obstruction: A prospective, randomized, double-blind, placebo-controlled trial	Anene	1996	USA	Prospective, randomized, double-blinded placebo-controlled	Chi square or Fisher exact, independentT test, Mann-Withney U test	66	<5y
Extubation failure due to post-extubation stridor is better correlated with neurologic impairment than with upper airway lesions in critically ill pediatric patients	Harel	1997	USA	Prospective, randomized, double-blinded controlled	Mann–Whitney rank sum test	23	0-10y
Effectiveness of dexamethasone in preventing extubation failure in preterm infants at increased risk for airway edema	Couser	1992	USA	Prospective, randomized, controlled	unpaired Student t test, chi-square analysis, and the Fisher Exact Test	50	<2m
Dexamethasone in the prevention of postextubation stridor in children	Tellez	1991	USA	Prospective, randomized, double-blinded controlled	Student T; Wilcoxon rank sum test; Chi square; Fisher E	153	0-…
Randomized comparative efficacy of dexamethasone to prevent postextubation upper airway complications in children and adults in ICU.	Malhotra	2009	India	Prospective, randomized, double-blinded placebo-controlled	Chi square or Fisher exact, independentT test	30	<12y
Nebulized fluticasone for preventing postextubation stridor in intubated children: A randomized, double-blind placebo-controlled trial	Prasertsan	2017	Thailand	Randomized, Double-Blind Placebo-Controlled Trial	Chi square or Fisher exact, Student T test, Mann-Withney U test	147	1y-15y

The pediatric population in the study of Malhotra et al. showed a significant reduction in failed extubation by CS (22). Drago et al. investigated the use of methylprednisolone in pediatric patients with acute respiratory distress syndrome (ARDS), they reported a reduced incidence of PES in the CS group as a secondary outcome. The need for epinephrine aerosols in case of PES in the CS group was significantly decreased when compared to the control group, 12% vs 44% respectively.(18) For extubation failure, Baranwal et al. reported a trend in reduction in the 24-hour pretreatment, but it did not reach statistical significance. A multivariate analysis identified long duration of intubation (more than 7 days) as most important risk factor. Cuffed tracheal tubes was an additional independent risk factor (17). No significant difference was found between the two groups regarding the need for epinephrine aerosols by Tellez et al (20). In the study of Cesar et al., there was no significantly higher rate of reintubation in the control group compared to CS group (8).

Adverse effects

Only a few studies recorded the adverse effects of CS treatment. In the group of Anene et al. one patient had an occult gastrointestinal bleeding in the CS group and two patients had hypertension, one of each intervention group (23). In the ARDS study of Drago et al. one patient developed hypertension in the steroid group, there was no higher risk for hyperglycemia between both groups (59% versus 50%) (18). Couser et al. noticed significantly more glucosuria in the dexamethasone group, with blood glucose levels varying between 120 and 175 $mg.dl^{-1}$. None of the patients required treatment (16).Hyperglycemia requiring treatment was reported only one time, by Baranwal et al, the glucose level was maximal $200mg.dl^{-1}$ (17). Two studies reported no increased risk of infection by CS treatment (17, 18).

The summary of the risk of bias assessment for the ten RCT's using the RoB2 tool is found in Table 3. The included studies of this systematic review show a moderate to high risk of bias.

Table 2

Summary of included articles

Administration route CS	Corticosteroid sheme	Control group	Setting: PICU/OR	Outcome: stridor/re-intubation/ aerosol therapy	Relative risk	CI (95%CI)	Funding
IV	IV dexamethasone 0,2mg/kg every 6h, starting 1 hour prior to extubation with or without nebulized L-epinephrine 0,5mg/kg (max of 5mg) every 4	yes, matched	PICU	PLE (Westley score) + reintubation	/	/	Not mentioned
IV	6x IV dxm 0.5mg/kg (24h before extubation every 6h); 3x IV sterile water + 3x IV dxm (1st 6h prior to extubation)	yes	PICU	PES (MWS) + Epinephrine aerosol + reintubation	RR, 2.02; 95 % CI, 1.05–3.88; p = 0.027) with		Not mentioned
IV	Methylprednisolon in 72h after intubation, tapered	yes	PICU	Epinephrine aerosol for post-extubation stridor			Grant support
IV	dxm 0,5mg/kg per dose (6-12h prior to extubation every 6h) 6 dose	yes	PICU	PES (croup score) + Epinephrine aerosols + reintubation	/	/	Not mentioned
IV	dxm 0,5mg/kg per dose (6-12h prior to extubation every 6h) 6 dose	yes	PICU	Stridor score	/	/	Not mentioned
IV	dxm 0.25 mg/kg/dose IV 6h before extubation , every 6h (4doses in total)	yes	PICU	PES + reintubation	/	/	Not mentioned
IV	dxm 0,5m/kg/dose (first dose 6-12h before extubation; 6 doses in total every 6h)	yes	PICU	PES + Epinephrine aerosol use + reintubation	0.63	0,3-1,31	Not mentioned
IV	dxm 0,5mg/kg (4h prior to planned extubation,at extubationand at 6h&12h after)	yes	PICU	PES + epinephrine aerosol use + reintubation	/	/	Not mentioned
Aerosol	Postextubation	yes	PICU	PES (MWS) + Epinephrine aerosol + NIPPV use + reintubation	/	/	Ramathibodi Research

Discussion

We conducted a systematic review regarding the prophylactic use of CS to prevent PES in a pediatric population. Theoretically, CS have an anti-inflammatory action. In clinical practice, they have been used in the prevention of PES for decades. CS treatment is currently based on clinical assessment of the physician, but in the literature, there is no consensus about their effectiveness and safety.

Five out of nine RCT's showed a significant effect of CS in prevention of PES or extubation failure. In the papers demonstrating a significant difference, it concerned patient populations considered at high risk of PES. First, Couser et al. included preterm neonates with a low birth weight which were ventilated for a longer period (16). Second, Anene et al. included patients who were intubated for more than 48 hours and did not exclude patients with an airway abnormalities (23). Third, in the ARDS study of Drago et al. patients were intubated for at least 72 hours before they were found eligible (18). Fourth, in 2014 Baranwal et al. proved a pretreatment of 24 hours prior to extubation was effective in reduction of PES compared to a 6-hour pretreatment. They found that intubation for more than 7 days and cuffed ETT were independent risk factors (17). In contrast, Malhorta et al. included patients with intubation of 24 hours or longer, but excluded those with airway abnormalities or disease. In the pediatric population, failed intubation was increased after longer intubation but not statistically increased (22). It is important to note that these papers had small study patient population, ranging from 30 to 66 patients, which may have caused underpowering of subgroup analyses.

Four papers failed to prove the effectiveness of CS to prevent PES or extubation failure. There are several reasons why these studies may not have been able to prove the success of CS. Tellez et al. stopped recruiting because preliminary analysis showed no significant difference in the occurrence of PES between the two groups, which may have

Table 3

Risk bias assessment (+: low risk; ?: some concerns; -: high risk)

Author name, year	Randomization process	Deviations from intended interventions (assignment)	Missing outcome data	Measurement of the outcome	Selective reporting	Overall risk of bias
Tellez, 1991	+	?	+	+	?	?
Couser, 1992	?	+	+	+	?	?
Anene, 1996	+	+	+	+	?	?
Harel, 1997	+	-	+	+	-	-
Cesar, 2009	+	-	?	+	?	-
Malhotra, 2009	+	+	+	?	-	-
Baranwal, 2014	+	+	-	+	?	-
Drago, 2015	?	+	+	+	?	?
Prasertsan, 2017	+	+	+	+	?	?

caused bias (20). An association was shown between extubation failure and neurological impairment by Harel et al. They found that extubation failure was related to neurological impairment instead of corticosteroid treatment (21). In this study, extubation failure was not caused by LE but rather by neurological impairment. The latter could be the reason for not being able to maintain a patent airway. Cesar et al. started treatment just one hour prior to extubation, what can cause that treatment was not as effective as 24-hour pretreatment, like Baranwal et al. suggested (8, 17). They also had a very high incidence of PES (69,75%), which could be explained by the definition of PES as a WCS of more than zero. In other studies PES was defined as a WCS of two or more, and four or more which needed intervention (8). We included one study with CS administration by inhalation. Prasertsan et al. used inhalation CS because of the topical effect, faster onset and less systemic absorption. This was the first study of nebulized CS in prevention of PES in pediatric patients, they did not reach a significant decrease in PES versus placebo. But they had lower scores of WCS in the first hours after extubation (19). Likewise, three RCT in adults with nebulized budesonide, did not demonstrate significant difference (24, 25).

Only a few complications were documented in the papers included in this review. Just one occult gastrointestinal bleeding was reported, three patients developed hypertension and hyperglycemia was reported in 19 patients. The low rate of complications could be explained by detection bias, because not all studies systematically registered adverse effects of CS. However, a recent systematic review and meta-analysis by Fernandes et al. did not found an increase in adverse events in short term use of CS in a pediatric population with acute respiratory illness (26).

There are some limitations to this systematic review. First, we could not retrieve full text of several potentially eligible papers. Ferrara et al. concluded that single dose prophylactic administration of dexamethasone 30 minutes prior to extubation did not improve the post-extubation course of infants (27). Courtney et al. concluded that a 24-hour pretreatment with dexamethasone had a limited effect on pulmonary function immediately following extubation (28). Second, the systematic screening of the literature was performed by only one author. However, in case of uncertainties, a second author (VDS) was consulted. Third, as in any systematic review, the conclusion is inherently limited by the quality of the underlying studies. The included studies were generally small, considerably varied in design, and all studies had moderate to high risk of bias. Hence, the evidence base with regard to prophylactic CS administration to prevent PES in children remains low.

Conclusion

Because currently prophylactic CS for PES are used at the discretion of the physician, we conducted a systematic review on this topic. We included nine RCT's, of which five showed a significant reduction in PES with the use of CS. RCT's showing benefit enrolled patients who could be considered at elevated risk of PES, including patients with prolonged intubation and preterm neonates with low

birth weight. Limited adverse events were reported, but were in general not systematically recorded. All included RCTs were relatively small and heterogeneous in design, and had a moderate to high risk of bias. Hence, although prophylactic CS may be effective and safe to reduce PES in children, the evidence base remains low.

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Appendix 1

MeSH (Medline):

"Adrenal Cortex Hormones"[Mesh] OR "Glucocorticoids"[Mesh] OR "Dexamethasone"[Mesh:NoExp] OR "Steroids"[Mesh:NoExp] OR glucocorticoid*[tiab] OR steroid*[tiab] OR dexamethasone[tiab] OR corticosteroid*[tiab] OR Prednisone [Mesh] OR Prednison*[tiab] OR Prednisolone[Mesh] OR Prednisolone[tiab] OR Methylprednisolone[Mesh] OR Methylprednisolone[tiab] OR Cortisone[Mesh] OR Cortisone[tiab] OR Hydrocortisone[Mesh] OR Hydrocortisone [tiab] OR Fludrocortisone[Mesh] OR Fludrocortisone[tiab] OR Budesonide[Mesh] OR Budesonide[tiab] OR Fluticasone[Mesh] OR Fluticasone[tiab] OR Ciclesonide[tiab] OR Triamcinolone[Mesh] OR Triamcinolone[tiab] OR Beclomethasone[Mesh] OR Beclomethasone[tiab] OR Flunisolide[tiab] OR Mometasone[Mesh] OR Mometasone[tiab]

AND

"Airway Obstruction"[Mesh:NoExp] OR "Laryngeal Edema"[Mesh] OR "airway obstruct*"[tiab] OR "Laryngeal edema"[tiab] OR "laryngeal oedema"[tiab] OR "Respiratory Sounds"[Mesh:NoExp] OR stridor[tiab]

AND

"Airway Extubation"[Mesh] OR "Intubation, Intratracheal"[Mesh] OR extubation[tiab] OR post-extubation[tiab] OR intubation[tiab]
= 350 hits (search articles included)

EMTREE terms (Embase):
'children younger than 6 years of age' OR '1 year of age' OR '1 year old' OR '2 years of age' OR '2 years old' OR '3 years of age' OR '3 years old' OR '4 years of age' OR '4 years old' OR '5 years of age' OR '5 years old' OR 'age under 1 year' OR 'age under 6 years' OR 'age under one year' OR 'age under six years' OR 'babies' OR 'baby'/exp OR 'baby' OR 'boy'/exp OR 'boy' OR 'boyhood' OR 'boys' OR 'child care'/exp OR 'child care' OR 'childhood'/exp OR 'childhood' OR 'children'/exp OR 'children' OR 'elementary school student'/exp OR 'elementary school student' OR 'elementary school students' OR 'elementary school'/exp OR 'elementary school' OR 'fifth grade' OR 'fifth grader' OR 'fifth graders' OR 'four years of age' OR 'four years old' OR 'fourth grade' OR 'fourth grader' OR 'fourth graders' OR 'girl'/exp OR 'girl' OR 'girls' OR 'girlhood' OR 'grade 1' OR 'grade 2' OR 'grade 3' OR 'grade 4' OR 'grade 5' OR 'grade 6' OR 'grade 7' OR 'grade one' OR 'grade two' OR 'grade three' OR 'grade four' OR 'grade five' OR 'grade six' OR 'grade seven' OR 'infant'/exp OR 'infant' OR 'infants'/exp OR 'infants' OR 'infantile' OR 'junior' OR 'juniors' OR 'kid' OR 'kids' OR 'kindergarten'/exp OR 'kindergarten' OR 'less than 6 years of age' OR 'month old' OR 'months old' OR 'neonate'/exp OR 'neonate' OR 'neonates' OR 'neo-nate' OR 'neo-nates' OR 'neonatal' OR 'neo-natal' OR 'neonatus'/exp OR 'neonatus' OR 'neo-natus' OR 'newborn care'/exp OR 'newborn care' OR 'newborn infant'/exp OR 'newborn infant' OR 'newborn'/exp OR 'newborn' OR 'newborns' OR 'nicu' OR 'one month of age' OR 'one month old' OR 'pediatric'/exp OR 'pediatric' OR 'pediatrics'/exp OR 'pediatrics' OR 'postterm' OR 'post-term' OR 'premature'/exp OR 'premature' OR 'pre-mature' OR 'preschool'/exp OR 'preschool' OR 'pre-school' OR 'preschool ages' OR 'pre-school ages' OR 'preschooler'/exp OR 'preschooler' OR 'pre-schooler'/exp OR 'pre-schooler' OR 'preschoolers'/exp OR 'preschoolers' OR 'pre-schoolers'/exp OR 'pre-schoolers' OR 'preterm' OR 'pre-term' OR 'school age'/exp OR 'school age' OR 'school aged' OR 'school'/exp OR 'school' OR 'schoolchild'/exp OR 'schoolchild' OR 'schoolchildren'/exp OR 'schoolchildren' OR 'second grade' OR 'second grader' OR 'second graders' OR 'seventh grade' OR 'seventh grader' OR 'seventh graders' OR 'sixth grade' OR 'sixth grader' OR 'sixth graders' OR 'term baby' OR 'term babies' OR 'term infant' OR 'term infants' OR 'third grade' OR 'third grader' OR 'third graders' OR 'three years of age' OR 'three years old' OR 'toddler'/exp OR 'toddler' OR 'toddlers'/exp OR 'toddlers' OR 'tot' OR 'tots' OR 'two years of age' OR 'two years old' OR 'under 1 year of age' OR 'under one year of age'

AND

'respiratory tract intubation'/exp OR 'extubation'/exp OR 'intubation':ab,ti OR 'extubation':ab,ti OR 'post-extubation':ab,ti

AND

'airway obstruction'/exp OR 'larynx edema'/exp OR 'stridor'/exp OR 'upper respiratory tract obstruction'/exp OR 'airway obstruction':ab,ti OR 'laryngeal edema':ab,ti OR 'laryngeal oedema':ab,ti OR 'upper respiratoy tract obstruction':ab,ti OR 'stridor':ab,ti

AND

'corticosteroid'/exp OR 'corticosteroid':ab,ti OR 'glucocorticoid'/exp OR 'glucocorticoid':ab,ti OR 'steroid'/exp OR 'steroid':ab,ti OR 'cortisone'/exp OR 'cortisone':ab,ti OR 'dexamethasone'/exp OR 'dexamethasone':ab,ti OR

‘prednisone’/exp OR ‘prednisone’:ab,ti OR ‘prednisolone’/exp OR ‘prednisolone’:ab,ti OR ‘methylprednisolone’/exp OR ‘methylprednisolone’:ab,ti OR ‘hydrocortisone’/exp OR ‘hydrocortisone’:ab,ti OR ‘fludrocortisone’/exp OR ‘fludrocortisone’:ab,ti OR ‘budesonide’/exp OR ‘budesonide’:ab,ti OR ‘fluticasone’/exp OR ‘fluticasone’:ab,ti OR ‘ciclesonide’/exp OR ‘ciclesonide’:ab,ti OR ‘triamcinolone’/exp OR ‘triamcinolone’:ab,ti OR ‘beclometasone’/exp OR ‘beclometasone’:ab,ti OR ‘flunisolide’/exp OR ‘flunisolide’:ab,ti OR ‘mometasone furoate’/exp OR ‘mometasone furoate’:ab,ti

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Cochrane

Search Name: Stridor
Last Saved: 12/07/2020 17:28:27
Comment:

ID Search
#1 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#2 MeSH descriptor: [Steroids] this term only
#3 MeSH descriptor: [Glucocorticoids] explode all trees
#4 MeSH descriptor: [Dexamethasone] this term only
#5 MeSH descriptor: [Prednisone] explode all trees
#6 MeSH descriptor: [Methylprednisolone] explode all trees
#7 MeSH descriptor: [Prednisolone] this term only
#8 MeSH descriptor: [Cortisone] explode all trees
#9 MeSH descriptor: [Hydrocortisone] explode all trees
#10 MeSH descriptor: [Fludrocortisone] explode all trees
#11 MeSH descriptor: [Budesonide] this term only
#12 MeSH descriptor: [Fluticasone] this term only
#13 MeSH descriptor: [Triamcinolone] explode all trees
#14 MeSH descriptor: [Beclomethasone] explode all trees
#15 MeSH descriptor: [Mometasone Furoate] this term only
#16 (glucocorticoid* OR steroid* OR dexamethasone OR corticosteroid* OR Prednisone OR Prednisolone OR Methylprednisolone OR Cortisone OR Hydrocortisone OR Fludrocortisone OR Budesonide OR Fluticasone OR Ciclesonide OR Triamcinolone OR Beclomethasone OR Flunisolide OR Mometasone):ti,ab,kw
#17 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18 MeSH descriptor: [Airway Obstruction] this term only
#19 MeSH descriptor: [Laryngeal Edema] explode all trees
#20 MeSH descriptor: [Respiratory Sounds] this term only
#21 (stridor OR laryngeal edema OR laryngeal oedema OR ‘airway obstruction’):ti,ab,kw
#22 #18 OR #19 OR #20 OR #21
#23 MeSH descriptor: [Airway Extubation] explode all trees
#24 MeSH descriptor: [Intubation, Intratracheal] explode all trees
#25 (post-extubation OR ‘post extubation’ OR intubation):ti,ab,kw
#26 #23 OR #24 OR #25
#27 MeSH descriptor: [Child] explode all trees
#28 MeSH descriptor: [Infant] explode all trees
#29 MeSH descriptor: [Pediatrics] this term only
#30 (‘children younger than 6 years of age’ OR ‘<1 year of age’ OR ‘<1 year old’ OR ‘2 years of age’ OR ‘2 years old’ OR ‘3 years of age’ OR ‘3 years old’ OR ‘4 years of age’ OR ‘4 years old’ OR ‘5 years of age’ OR ‘5 years old’ OR ‘age < 1 year’ OR ‘age < 6 years’ OR ‘age < one year’ OR ‘age < six years’ OR ‘babies’ OR ‘baby’ OR ‘boy’ OR ‘boyhood’ OR ‘boys’ OR ‘child care’ OR ‘childhood’ OR ‘children’ OR ‘elementary school student’ OR ‘elementary school students’ OR ‘elementary school’ OR ‘fifth grade’ OR ‘fifth grader’ OR ‘fifth graders’ OR ‘four years of age’ OR ‘four years old’ OR ‘fourth grade’ OR ‘fourth grader’ OR ‘fourth graders’ OR ‘girl’ OR ‘girls’ OR ‘girlhood’ OR ‘grade 1’ OR ‘grade 2’ OR ‘grade 3’ OR ‘grade 4’ OR ‘grade 5’ OR ‘grade 6’ OR ‘grade 7’ OR ‘grade one’ OR ‘grade two’ OR ‘grade three’ OR ‘grade four’ OR ‘grade five’ OR ‘grade six’ OR ‘grade seven’ OR ‘infant’ OR ‘infants’ OR ‘infantile’ OR ‘junior’ OR ‘juniors’ OR ‘kid’ OR ‘kids’ OR ‘kindergarten’ OR ‘less than 6 years of age’ OR ‘month old’ OR ‘months old’ OR ‘neonate’ OR ‘neonates’ OR ‘neo-nate’ OR ‘neo-nates’ OR ‘neonatal’ OR ‘neo-natal’ OR ‘neonatus’ OR ‘neo-natus’ OR ‘newborn care’ OR ‘newborn infant’ OR ‘newborn’ OR ‘newborns’ OR ‘NICU’ OR ‘one month of age’ OR ‘one month old’ OR ‘pediatric’ OR ‘pediatrics’ OR ‘postterm’ OR ‘post-term’ OR ‘premature’ OR ‘premature’ OR ‘preschool’ OR ‘pre-school’ OR ‘preschool ages’ OR ‘pre-school ages’ OR ‘preschooler’ OR ‘pre-schooler’ OR ‘preschoolers’ OR ‘pre-schoolers’ OR ‘preterm’ OR ‘pre-term’ OR ‘school age’ OR ‘school aged’ OR ‘school’ OR ‘schoolchild’ OR ‘schoolchildren’ OR ‘second grade’ OR ‘second grader’ OR ‘second graders’ OR ‘seventh grade’ OR ‘seventh grader’ OR ‘seventh graders’ OR ‘sixth grade’ OR ‘sixth grader’ OR ‘sixth graders’ OR ‘term baby’ OR ‘term

babies' OR 'term infant' OR 'term infants' OR 'third grade' OR 'third grader' OR 'third graders' OR 'three years of age' OR 'three years old' OR 'toddler' OR 'toddlers' OR ' tot' OR 'tots' OR 'two years of age' OR 'two years old' OR 'under 1 year of age' OR 'under one year of age'):ti,ab,kw

#31 #27 OR #28 OR #29 OR #30

#32 #17 AND #22 AND #26 AND #31

#33 #17 AND #22 AND #26 = 87hits

Appendix 2

Tellez 1991:

- RCT (double blinded)
- USA: PICU
- 153 participants (divided in 3 age groups: >1y; 1-5y; >5y) no upper limit mentioned
- Exclusion of pharyngeal or laryngeal infection, surgical trauma to the upper airway or history of upper airway obstruction
- Including patients with multiple intubations
- Dexamethasone 0,5m/kg/dose (first dose 6-12h before extubation; 6 doses in total every 6h)
- PES + Epinephrine aerosol use + reintubation; RR 0,63 (CI 95% 0,3-1,31) → no statistical significance; the study stopped early because of no significance and enlarging the groups was unethical and unpractical
- Adverse effects CS not investigated
- The incidence of PES is 25% → higher than other studies of short term ETT; because of the minimal 6h pretreatment, less short term intubations were included

Couser 1992:

- RCT (blinded, placebo controlled)
- USA: PICU
- 50 participants: under 2months of age
- Exclusion: previously failed extubation or who required high-frequency jet ventilation, congenital anomalies of the central airways such as laryngotracheal malacia or anomalies of the lung parenchyma (e.g., congenital diaphragmatic hernia, cystic adenomatoid malformation, sequestration)
- Inclusion: high risk neonatal population: low birth weight infants who required mechanical ventilation and had either traumatic or multiple ETIs or if the duration of ETI was >14 days; preterm subjects
- IV dexamethasone 0.25 mg/kg/dose IV 6h before extubation , every 6h (4doses in total)
- PES + reintubation: + lung function tests:

stridor = a high-pitched inspiratory sound associated with signs of upper airway obstruction (prolonged inspiratory phase, nasal flaring, suprasternal, sternal, or intercostal retractions, and the use of accessory respiratory muscles); reintubation = stridor appeared severe and was associated with bradycardia (heart rate <100 beats/min), oxygen desaturation (arterial oxy- gen saturation <85% by pulse oximetry despite a fraction Of inspired oxygen between 0.8 and 1.0), and if they failed to respond to racemic epinephrine (2.25% solution) aerosol treatment or required frequent bag-and-mask ventilation → Stridor ($p < 0.01$). four control infants required reintubation for significant stridor 6, 8, 10, and 21 hours, respectively, after extubation.

→ dynamic compliance was significantly better in the dexamethasone group

- Adverse effects of CS: no significant changes in systemic blood pressure; glucosuria was present in more dexamethasone-treated patients than in the control patients ($p < 0.05$). Glucose intolerance was short-lived and did not require any treatment.
- Effective in risk population: low birth weight, high risk preterm infants

Anene 1996:

- RCT (double blinded, placebo controlled)
- USA: PICU
- 66 participants: age under 5 years
- Exclusion: laryngotracheal infections
- Inclusion: only first elective extubation; airway abnormalities (similar in both groups); intubation duration >48 hours
- IV Dexamethasone 0,5mg/kg per dose (6-12h prior to extubation every 6h) 6 doses in total→
- PES + Croup Score + Epinephrine aerosols (in Croup score > or =2) + helium-oxygen gas mixture (croup score > or =4 without improvement after 3 doses of aerosolized racemic epinephrine) + reintubation → lower frequency of

stridor, croup score and pulsus paradoxus with no significance difference; fewer epinephrine aerosols (p<0,0001) + fewer reintubation (p<0,01)
- Adverse effects CS: hypertension, hyperglycemia, gastrointestinal bleeding → 1 patient in the CS group had an occult gastrointestinal bleeding and one patient of each group had hypertension

Harel 1997:

- RCT (double blinded, placebo controlled)
- USA: PICU
- 23 participants: age 0-10 years
- Inclusion: failed extubation
- IV Dexamethasone 0,5mg/kg per dose (6-12 hours prior to extubation, every 6 hours) 6 doses in total
- Stridor score (depending on stridor, cyanosis, sternal retractions, respiratory rate and heart rate) → highest score was used for analysis → no statistical significant difference of stridor score between groups; although the stridor score was related to the success of extubation (p=0,0027)
- Adverse effects of CS: not mentioned
- Limitations: very small number
- Failure of extubation was more correlated with neurological impairment → CS would not be effective if that is the cause instead of an upper airway obstruction

Malhotra 2009:

- RCT (double blinded, placebo controlled)
- India: ICU (adults + pediatric population)
- 30 children: under 12 year
- Inclusion: under 10years old intubation with uncuffed ETT (intubations were performed by qualified experienced anesthetists in the OR or in Accidental Emergency)
- Exclusion: upper airway disease, neck surgery, anatomical deformity of upper airways, extubation during the same hospitalization
- IV dexamethasone 0,5mg/kg/dose (4 hours prior to planned extubation, at extubation and at 6 hours and 12 hours after extubation)
- PES + Epinephrine aerosol + reintubation:
    - Assessment of Airway status in adults and children: 1. Laryngeal Dyspnea; 2. Laryngeal Stridor; 3.Laryngeal Edema
    - Scoring for stridor in children: 0 =No stridor; 1=Stridor while crying ; 2=Stridor at rest; 3= Severe Biphasic chest retractions.

→ Pediatric: significant difference in failed extubation (p=0,019); highly statistical significance in Airway assessment status (p=0.004).Laryngeal edema was more in Control group (63.33%) in children as compared to Dexamethasone group (26.67%)
- Long duration of intubation > 24 hours → patients at high risk

Cesar 2009:

- RCT (double blinded, placebo controlled)
- Brazil: PICU
- 64 participants: age 1d-12y
- Exclusion: vocal cord abnormalities, anatomic abnormalities of the upper airways before intubation
- Inclusion: multiple intubation attempts
- IV dexamethasone 0,2mg/kg every 6h, starting 1 hour prior to extubation with or without nebulized L-epinephrine 0,5mg/kg (max of 5mg) every 4 hours → 4 groups of 16 patients
- PES (WCS >0) + Reintubation → PES overall 68,75%; no significant difference between the four groups, the same for reintubation
- Adverse effects of CS not mentioned
- Limitations: very high incidence of PES = 68,75% → WCS >0?; start CS scheme 1 hour prior to extubation

Baranwal 2014:

- RCT (double blinded, placebo controlled)

- India: PICU
- 124 participants: age 3months till 12 years
- Exclusion: actual or potential poor airway reflexes (e.g., Guillain–Barre syndrome with unstable airway, tetanus, etc.), Glasgow Coma Score (GCS) < 8 (only best motor and eye responses), congenital anomalies, infection, burns, trauma and surgery involving airway, history of previous tracheal intubation or tracheostomy, chronic lung disease
- Inclusion: age [3 months and < 12 years, intubation for > 48 h, and anticipated first planned extubation during the next 24 h
- IV 24 hours prior to extubation dexamethasone 0.5mg/kg/dose every 6 hours (in total 6 doses) versus 6 hours prior to extubation 0,5mg/kg/dose every 6 hours (in total 3 doses)
- PS (MWS) + Epinephrine aerosol + reintubation → RR, 2.02; 95 % CI, 1.05–3.88; p = 0.027; Re-intubation: 24hPD reduced this by half, this was not statistically significant (24hPD, 5/61 versus 6hPD, 9/58; RR, 1.09; 95 % CI, 0.96–1.25); 24hPD delayed reintubation as well, with a median gap of 12 h (range 3–13 h) since extubation among 24hPD patients, versus 6 h (range 0 min to 36 h) among 6hPD patients
- Multivariate analysis identified intubation: >7 days as the most important independent risk factor, others being cuffed tracheal tubes and not having received 24hPD.
- Adverse effects of CS: One patient developed hyperglycemia (maximum blood sugar, 200 mg/dl) at 12 h of extubation among 24hPD patients and needed insulin infusion for 4 h. None developed upper gastrointestinal hemorrhage, hypertension, signs of infection or any other event attributable to steroid during 48 h of observation period.
- Limitations: exclusion previous intubation; ¾ PES → high incidence (due to stratified score system?)

Drago 2015:

- RCT (double blinded, placebo controlled)
- USA: PICU
- 35 participants: age from 1 month till 18 years
- Inclusion: Mechanical ventilation > 72 hours
- Exclusion: receiving glucocorticoids, were terminally ill or on hospice care, were immunosuppressed, or had extensive burns, adrenal insufficiency, vasculitis, diffuse alveolar hemorrhage, invasive fungal infection, chronic liver disease, or gastrointestinal bleed within the past month, or conditions with estimated 6-month mortality of 50% or higher.
- IV Methylprednisolone in 72 hours after intubation (methylprednisolone loading dose of 2 mg/kg infused over 15 minutes, followed by continuous infusions 1 mg/kg/d on days 1–7, 0.5 mg/kg/d on days 8–10, 0.25 mg/kg/d on days 11 and 12, and 0.125 mg/ kg/d on days 13 and 14. Patients in the placebo group received equivalent volumes of 0.9% saline. Patients received the full 14-day steroid regimen if they required mechanical ventilation for 7 days or longer. If patients were extubated between days 1 and 7, they were advanced to day 8 of therapy (methylprednisolone 0.5 mg/kg/d) and then tapered according to protocol
- Epinephrine aerosol for post-extubation stridor → Fewer patients needed epinephrine aerosol for post-extubation stridor (p=0,04), 12% vs 44% → based on clinical condition (observer dependent)
- Adverse effects of CS: Hypertension developed in one patient in the steroid group, did not increase the risks of hyperglycemia or nosocomial infections
- Limitations: PES not primary outcome (ARDS study), no objective score for PES used

Prasertsan 2017:

- RCT (Double blinded, placebo controlled)
- Thailand: PICU
- 147 participants: age 1m-15y
- Exclusion: palliative care, airway abnormalities such as subglottic stenosis, neuromuscular weakness defined as negative inspiratory force (NIF) less than –30 cm H2O (20), patients who were planned for noninvasive positive pressure ventilator (NIPPV) after extubation, accidental extubation
- Inclusion of multiple intubations: no difference between groups
- Inhalation CS post-extubation (1,000 µg of fluticasone or normal saline solution (NSS))→ Nebulized corticosteroids have a topical effect, faster onset, and less systemic absorption than systemic corticosteroid
- MWS till 6u post-extubation → no significant difference between the two groups; however they see a difference in early MWS between the groups
- Adverse effects of CS not mentioned → because of topical administration?
- Limitations: evaluation bias by different observers; excluding accidental extubation; few patients intubated for longer than 48 hours; short term of observation (only 6 hours after extubation; although no reintubation observed till discharge)