Role of Parenteral Steroids to Prevent Extubation Failure in Ventilated Children

The following piece (in italics) is presented with kind permission from the *Archimedes* section of *Archives of Disease in Childhood*(1). This is followed by examination of the evidence along the lines of EURECA.

ARCHIMEDES

Lukkassen MA, Markhorst DG. Arch Dis Child 2006; 91; 791-793.

Clinical scenario: *John, a 4-year-old boy, has been mechanically ventilated for three days during recovery from a blunt chest trauma. According to his level of ventilator support, he is considered to be ready to be extubated. The previous patient had to be reintubated as a result of postextubation laryngeal edema. You wonder whether corticosteroids may reduce this risk of extubation failure.*

Structured clinical question: *In mechanically ventilated children (patient), does corticosteroid administration (intervention) reduce the chance of reintubation due to laryngeal edema (outcome)?*

Search Strategy and Outcome

Secondary sources: *Cochrane Database of Systematic Reviews: 1; limited to newborn infants: 1; PubMed clinical queries: "Respiration, Artificial" [MESH] AND (hydroxycorticosteroids) [MESH] AND systematic; 1 reference not related to the question. ("Intubation, Intratracheal" [MeSH]) AND systematic[sb] AND (Hydroxycorticosteroids) [MESH]; no references.*

PubMed: (anti-inflammatory agents OR anti-inflammatory agents/ therapeutic use OR anti-inflammatory agents/therapy OR hydroxycorticosteroids) AND systematic[sb]) AND ("intubation, intratracheal" [MeSH] OR "respiration, artificial" [MeSH]); 25 references, 2 relevant studies. ("reintubation" or ("failure" and "extubation")) AND (anti-inflammatory agents or anti-inflammatory agents/therapeutic use OR anti-inflammatory agents/therapy OR hydroxycorticosteroids); 30 references, with 4 relevant. "reintub" AND "steroids"; 30 references, 7 relevant of which 1 systematic review, 4 studies had been analysed in systematic reviews.*

COMMENTARY*: The outcome, requirement for endotracheal reintubation, is of clinical importance in the spectrum of those relating to paediatric intensive care. Pediatric intensive care patients with failed intubation have longer hospital, paediatric intensive care, and ventilator courses, leading to additional costs, risks, and patient burden. The risk of reintubation in this patient group is above 10% (2-4). In the ex-preterm intubated newborn, prophylactic corticosteroids reduce the need for reintubation. In the pediatric population, the benefit of prophylaxis is less clear. The overall benefit is estimated at 1 in 59 children succeeding extubation when they would have failed without corticosteroid prophylaxis. However, the study size means that the true value may be that as few as 11 children need to be treated, or indeed that treating 17 children causes one an additional failure that would not have occurred if a placebo had been given. Limiting prophylaxis to children at risk for developing postextubation laryngeal oedema (e.g., multiple airway manipulations, or failed prior extubation), the benefit seems to improve. In this patient group, five children (95% CI 3 to 13) have to be treated to avoid one reintubation.*

Dexamethasone is a potent glucocorticoid with many effects beyond reducing airway oedema. The disturbance to glucose metabolism is well demonstrated, although the clinical relevance has yet to be shown. Prophylactic use of dexamethasone was not associated with the development of hypertension in neonates. Anene et al noted one patient treated with gastrointestinal bleeding. The

EURECA CONCLUSIONS IN THE INDIAN CONTEXT

- There is no evidence that parenteral steroids prevent 'extubation failure' in children and neonates, although data are limited.
- Multiple doses of steroids, administered at least 12 hours prior to extubation are beneficial in adults.

drug is not without side effects and defining the group of children in whom it is most likely to be effective seems desirable, since the trend towards a favourable effect of prophylaxis is most expressed in this group. The studies had relatively few patients, and showed significant heterogeneity. As a result the power of the data is limited. Furthermore, the dose regimen varied between the studies, varying from a single low dose immediately prior to extubation to multiple high doses given 24 hours prior to extubation.

A well designed, adequately powered prospective study limited to patients at risk for extubation failure, to assess the benefits and side effects of prophylactic steroid treatment in this group of paediatric patients is warranted to draw firm conclusions. Awaiting such a trial one could argue that, given the impact of endotracheal reintubation, the costs associated with failed extubation, the relative low costs of accepting a significant NNT, and the absence of clinical significant side effects, prophylactic multiple dose corticosteroid administration prior to extubation in high risk neonatal and paediatric patients can be defended. Given the lack of effect in low risk patients and potential side effects, it seems reasonable to withhold steroid prophylaxis in these patients.

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Relevance: The clinical question presented here crops up with unfailing regularity in pediatric practice, especially in intensive care units. Many pediatricians routinely administer and/or advocate parenteral corticosteroids (usually dexamethasone in varying doses and durations), to prevent post-extubation upper airway obstruction. Therefore, the question in this section from Archimedes is relevant to our setting. As the intervention (parenteral steroids) is easy to administer, affordable, readily accessible, with outcomes that can be assessed clinically or with basic laboratory support, it is all the more important to determine whether it is efficacious and safe (or otherwise). The outcomes relevant to the clinical question are the need for reintubation (extubation failure); surrogate outcomes could be incidence of stridor, duration of intubation, length of ICU stay, *etc*.

Current Best Evidence with Critical Appraisal: The Cochrane review published in 2008(2) included a comprehensive search till April 2007. Hence, an additional broad (sensitive) Pubmed search from 1 April 2007 to 18 April, 2008 was conducted. The search strategy 'steroid extubation' yielded 15 citations, and 'steroid intubation' yielded 97 citations. From the latter, one additional relevant randomized trial in adults(3), one publication in Chinese(4) on children and four comments/ editorials were identified. The former yielded an additional e-abstract of a systematic review in adults, due for publication next month(5) and an editorial comment. A Pubmed search for systematic reviews using the terms 'steroid extubation' yielded 14 citations of which 5 were relevant(5-9). Interestingly, the latest Cochrane Review(2) did not appear in any of the Pubmed searches, probably because it was published just two days back. Best BETs had the same publication as Archimedes(1). The four older systematic reviews(6-9) analysed data from the same trials but presented them somewhat differently. Thus the updated Cochrane review(2) and recent additional trial(3) comprise current best evidence.

The Cochrane review concluded that overall, steroids have no beneficial effect on the need for reintubation or development of stridor in any age group. This is in contrast to the previous version that reported beneficial effect on stridor in children(6). Post-hoc sub-group analysis of the updated review suggested that multiple doses and administration

more than six hours prior to extubation reduced the risk of stridor, although there was no beneficial effect on reintubation.

I re-analysed the meta-analysis with inclusion of the data from the recent trial in adults(3); this shows that in adults, there is a clear benefit of steroids on the development of stridor (RR 0.47, 95% CI 0.22 to 0.99), but not on the need for reintubation (RR 0.48, 95% CI 0.19 to 1.22). This trial consisted of four doses of intravenous dexamethasone at six-hour intervals, starting 24 hours prior to extubation. This reiterates the belief that multiple doses started well before extubation may have a beneficial effect.

Next, I performed meta-analysis of data from trials that used multiple doses of steroid at least 12 hours prior to extubation. There were no such trials in neonates and children; however there were three randomised controlled trials in adults(4,10,11). Steroids clearly reduced the risk of requiring reintubation (RR 0.20, 95% CI 0.08-0.47) and development of stridor (RR 0.19, 95% CI 0.12-0.30). The respective numbers need to treat (NNT) are 20 (95% CI 14-50) and 5 (95% CI 4-7).

Thus hitherto unpublished current best evidence shows a beneficial effect of multiple doses of steroids administered well before extubation in adult patients, although the latest Cochrane review does not reflect this conclusion. It is not clear whether this result can be directly extrapolated to neonates and children, considering that airway geometry and site of post-extubation upper airway obstruction are different. However, in the absence of well designed randomised controlled trials using multiple doses several hours before extubation, this question is open to research. It must be remembered that trials in adults were conducted observing limited beneficial effects seen in children; it appears that the wheel has come a full circle and the incontrovertible evidence in adults must lead to new trials in children and neonates.

Extendibility: Although none of the trials in the various systematic reviews were performed in our country, the clinical setting, population groups and nature of intervention are not uncommon. Therefore, the evidence can be extended to our setting. Although there is no conclusive data to prove (or disprove) that the intervention is beneficial in the pediatric age group, the analysis in EURECA suggests that it is beneficial in adults.

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