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Editorial

Rebound stridor in children with croup after nebulised adrenaline: does it really exist?

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Laryngotracheobronchitis is a common childhood illness affecting 3% of children. Most of the affected children are aged between 6 months and 3 years, with a peak incidence of 60 per 1000 child-years in those children aged between 1 and 2 years [1]. Epidemiological studies suggest that 1–5% of children with croup are admitted to hospital and 2–3% of those admitted children, require intubation [2]. Death is extremely rare and has been estimated to occur in no more than 1 in 30000 cases [2]. Parainfluenza (types 1 and 3), and influenza A and B are the most common viral agents causing croup. Respiratory syncytial virus (RSV), rhinovirus, coronavirus, metapneumovirus and adenovirus are also responsible for this illness. There is seasonality to the prevalence with more presentations in the autumn. There is an annual pattern influenced by the variability of the viruses in the community for that year [2].

Croup is characterised by a "barking" cough, hoarse voice, stridor and respiratory distress caused by generalised airway inflammation and oedema of the upper airway mucosa. Most children have mild illness which resolves spontaneously without any specific treatment. However, some children have severe illness with stridor, respiratory distress and hypoxaemia requiring intubation. Current evidence strongly supports the use of glucocorticoids for the management of croup [3]. Previously it was felt that steroids took up to 6 h to have an effect on the airway [4], but a recent Cochrane review concluded that glucocorticoids improve croup symptoms at 2 h with the effect lasting at least 24 h [3]. Glucocorticoids also reduce rates of return visits, admissions and readmissions. When treated with placebo, 204 out of every 1000 children will return for medical care. When treated with glucocorticoids, 74–153 out of every 1000 children will return for medical care [3]. Glucocorticoids reduce the length of stay by 15 h (range 6–24 h), but make no difference to the need for additional treatments. Dexamethasone 0.15 $mg \cdot kg^{-1}$ or prednisolone 1 $mg \cdot kg^{-1}$ would be the recommended treatment dosing [2], although other guidelines suggest doses up to 0.6 $mg \cdot kg^{-1}$ of dexamethasone [3].

Nebulised adrenaline/epinephrine is recommended for use in severe and life-threatening croup [5], although some guidelines use it for those children with moderate symptoms [6]. Nebulised adrenaline has been associated with a clinically and statistically significant transient reduction in croup symptoms 30 min post-treatment [5] and can "buy time" for steroids to act. Children with croup develop swelling of inner mucosal layers of the larynx and trachea. Nebulised adrenaline is thought to act by stimulating α-adrenergic receptors in subglottic mucous membranes, producing vasoconstriction and decreased mucosal oedema. The clinical effect is sustained for at least 1 h, but disappears after 2 h. Studies of nebulised adrenaline treatment of croup have used both racemic and L-adrenaline. One small trial found that L-adrenaline (5.0 mL, 0.1% (1:1000)) was as effective and safe as racemic adrenaline (0.5 mL, 2.25%) [7]. When racemic and L-adrenaline are compared, there is no difference in croup score at 30 m (standardised mean difference 0.33, 95% CI –0.42–1.08), but at 2 h L-adrenaline shows a small reduction in croup score compared

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with racemic adrenaline (standardised mean difference 0.87, 95% CI 0.09–1.65) [5].

There is a widespread belief amongst clinicians that such treatment can cause rebound phenomenon [8]. This was first suggested in 1978 [8] and 40 years on, continues to be mentioned as a possibility in publications in 2018 [1].

Rebound is defined as a temporary deviation from a normal state in the opposite direction following an abrupt removal or discontinuation of a variable, such as a treatment suddenly discontinued after long-term use, a passive resistance that is released suddenly, an undershoot in an effort to restore balance or homeostasis, or a condition wherein the maximum therapeutic effect is reached and the opposite effect ensues [9]. The rebound phenomenon occurs when the sudden discontinuation of a medication results in the relapse of symptoms that are worse than those before the treatment. Examples of rebound phenomenon include Stewart–Holmes test for cerebellar lesions [10] and Somogyi phenomenon [11].

We hypothesise that children with croup, following treatment with nebulised adrenaline may develop re-emergence of their initial symptoms, which are milder than at initial presentation and no worse than at baseline and that rebound of symptoms in croup does not occur after treatment with nebulised adrenaline. We performed a literature search to ascertain the degree of re-emergence symptoms and to determine if it were worse than baseline. The search was completed independently by two authors (M.S. and S.E.).

Search question

Do children with croup (patient group) when treated with nebulised adrenaline (intervention) develop re-emergence of stridor, worse than the initial baseline presentation (comparison) as defined by changes in symptoms score (outcome)?

Search strategy

Secondary sources: the Cochrane library was searched in September 2018 with the terms Croup and Adrenaline OR Epinephrine. One relevant review [5] was identified. The review included eight studies. Primary sources: MEDLINE was searched *via* PubMed using following terms Croup OR Laryngitis AND Adrenaline OR Epinephrine OR rebound stridor. Inclusion criteria were that studies included children between the ages of 0 and 18 years. 41 clinical trials were retrieved. A further two studies [12, 13] were considered relevant, in addition to the eight studies included in the Cochrane review. Summaries of the papers are presented in the table 1.

Discussion

The management of children with croup has had several controversies over the decades. In 1988, a review by Couriel [21] emphasised the lack of high-quality studies to aid management. Nebulised adrenaline was advocated only in children with impending airway obstruction, due to the transient improvement and possibility of rebound. The benefit of steroids in the management was not clearly established at that time and hence most early studies compared treatments of nebulised adrenaline with placebo or racemic adrenaline *versus* L-adrenaline.

Lenny and Milner [8] proposed the possibility of rebound phenomenon in children with acute viral croup treated with a nebulised α-adrenergic stimulant. The authors studied the total airway resistance before and after administration of nebulised phenylephrine in eight children. Prior to nebulisation, two drops of 0.05% xylometazoline were instilled in each nostril to ensure full nasal patency and children were sedated with 80 $mg \cdot kg^{-1}$ chloral hydrate. Seven out of eight children who were treated with nebulised phenylephrine showed improvement clinically and in terms of airway resistance. One child who did not show improvement was later was diagnosed with acute epiglottitis. The authors reported that improvement was transient and the airway resistance returned to pre-treatment levels within 30 min, which was hypothesised as a possible rebound phenomenon.

Over the following 40 years, the 10 studies identified here are very reassuring in that rebound does not exist and that although symptoms may return after the use of nebulised adrenaline, no study has reported the symptoms as being worse than baseline. If steroids are used as well then, as their effect starts to impact the upper airway at 2 h post-administration, this reduces any re-emergence of symptoms post-adrenaline as that effect wears off after 1–2 h.

A small underpowered study from 1973 by Gardner *et al.* [20], reported before the advent of the widespread use of steroids, was a retrospective review and this, not surprisingly, failed to substantiate a decrease in either hospitalisation or symptoms resulting from treatment with nebulised adrenaline. They did, however, acknowledge that adrenaline may be of therapeutic value in some patients with croup depending on the aetiological agent but may simply be the addition of moisture to the airways.

Three small studies [17–19], involving 48 children in total, showed significant initial improvement using nebulised adrenaline compared to placebo with some return of symptoms but no rebound reported. The following studies started using steroids in their design and recruited larger numbers but in children with more severe croup. No rebound of symptoms is described and an effect of the

Table 1 *Summary of the 10 articles examining re-emergence of symptoms after nebulised adrenaline use in croup*

Citation [ref.], year	Study population	Study type	Outcome	Comments
Eghbali [12], 2016	174 children between age of 6 months and 6 years. 87 children received placebo and 87 children received nebulised L-adrenaline (0.5 mg·kg^{-1} per dose). A single dose of *i.m.* dexamethasone 0.6 mg·kg^{-1} (maximum 8 mg) was administered to all.	Randomised double blind clinical trial	Significant reduction in mean croup score (Westley croup score) in children who received L-adrenaline ($p<0.009$).	Children treated with nebulised L-adrenaline showed continued decrease in croup score until 120 min. No rebound effect demonstrated in both study groups.
Weber [13], 2001	29 children with moderate to severe croup (modified Taussig croup score >5). Cool humidified oxygen and *i.m.* dexamethasone 0.6 mg·kg^{-1} administered to all children. 15 children randomised to nebulised racemic adrenaline 0.5 mL in 2.5 mL of normal saline for 3 h. 14 children randomised to 3 h of Heliox (blend of 70% helium and 30% oxygen) gas therapy for 3 h, with nebulised saline as placebo.	Randomised double blind clinical trial	Improvement in croup scores in both groups, with no overall statistically significant difference.	No deterioration of croup score to above score at presentation.
Kristjansson [14], 1994	54 children with mild to moderate croup. 25 children received racemic adrenaline and 29 children placebo.	Randomised double blind clinical trial	Children in both groups showed improvement. Children who received racemic adrenaline were significantly better than placebo in terms of improvement in total clinical score, inspiratory stridor, retractions and air entry. Relapse phenomenon was seen in 35% of children in the treatment group and 25% in placebo group. No child was clinically worse at 2 h after treatment than before treatment.	Authors reported relapse rather than rebound. The re-emergence of symptoms was higher in adrenaline group than placebo, but symptoms were no worse than baseline.

Continued

Table 1 *Continued*

Citation [ref.], year	Study population	Study type	Outcome	Comments
Fernandez [15], 1993	66 children hospitalised for croup. Children were randomised into four groups. Group 1: nebulised L-adrenaline and placebo (*i.m.*). Group 2: nebulised saline and placebo (*i.m.*). Group 3: nebulised saline and dexamethasone (*i.m.*). Group 4: nebulised L-adrenaline and dexamethasone (*i.m.*).	Randomised double blind clinical trial	Nebulised adrenaline was more beneficial than saline ($p<0.05$). No statistically significant improvement in the group treated with dexamethasone when compared with the group treated with the placebo *i.m.* injection.	No deterioration of croup score to above the score at presentation.
Waisman [7], 1992	Children between 6 months and 6 years of age with modified Downes and Rahaely Raphaely score>6. 16 children randomised to receive racemic nebulised adrenaline and 15 nebulised L-adrenaline. *i.m.* dexamethasone 0.6 mg·kg^{-1} given to children with a score >8.	Randomised double blind clinical trial	Significant reduction in croup scores in both groups at 30 min.	Re-emergence of croup symptoms with slight increase in croup scores at 60 min but no worse than baseline.
Kuusela [16], 1988	72 children hospitalised for croup were randomised to receive a single dose of 0.6 mg·kg^{-1} of *i.m.* dexamethasone or placebo. Subsequently the same patients were randomised to receive either nebulised racemic adrenaline or saline by inhalation.	Randomised double blind clinical trial	Children who received dexamethasone and racemic adrenaline had the lowest scores by all evaluations at 6 and 12 h. Only cough score at 6 h was significantly better in dexamethasone and racemic adrenaline group than the dexamethasone and saline group.	The authors conclude that a single *i.m.* injection of dexamethasone is beneficial in acute spasmodic croup. Nebulised racemic adrenaline is also effective, but the effect is less remarkable in patients treated with dexamethasone. The study does not provide clinical data at 30 min or 60 min when racemic adrenaline is likely to be beneficial.

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Table 1 *Continued*

Citation [ref.], year	Study population	Study type	Outcome	Comments
Fogel [17], 1982	14 children with croup who had persistent inspiratory stridor at rest 20–30 min after sterile saline mist therapy were randomised to receive racemic adrenaline by nebulisation alone or racemic adrenaline by nebulisation with IPPB.	Randomised double blind clinical trial	Highly significant reduction in croup score ($p<0.001$) in both groups at 30 and 60 min, but no significant difference at 90 and 120 min.	None of the children received steroids. No deterioration of croup score to above the score at presentation.
Corkey [18], 1981	14 hospitalised children with acute infectious croup were randomised to receive nebulised distilled water (group I) or racemic adrenaline (group II).	Randomised double blind clinical trial	Group II children who received racemic adrenaline showed a statistically significant improvement ($p<0.005$) in both objective radiological assessment of tracheal diameter and subjective clinical score.	None of the children received steroids. No deterioration of croup score to above the score at presentation.
Westley [19], 1978	20 hospitalised children between 4 months and 5 years with acute croup and persistent stridor at rest. 10 children randomised to receive 2.25% racemic adrenaline and 10 children received nebulised normal saline as placebo.	Randomised double blind clinical trial	Racemic adrenaline group showed significant reduction in mean croup score 10 and 30 min after treatment compared with placebo ($p<0.01$).	Authors report no statistically significant difference in croup score at 120 min; however, analysis of data shows that it was no worse than pre-treatment level.
Gardner [20], 1973	20 children evaluated. 10 received racemic adrenaline and 10 received placebo.	Controlled double blind trial	Of the 10 children who showed a significant improvement five received racemic adrenaline and five placebo. All three children who showed mild improvement had received racemic adrenaline. Of seven children who had no improvement two received racemic adrenaline and five received placebo.	The authors concluded that apparent effectiveness of racemic adrenaline might be related to nebulisation of moisture rather than direct effect of the drug. None of children received steroids. No deterioration of croup score to above the score at presentation.

i.m.: intramuscular; IPPB: intermittent positive pressure breathing.

steroids reducing any re-emergence of symptoms is becoming clearer [7, 15, 16] (see table 1).

Kristjansson *et al.* [14] reported re-emergence of symptoms in 35% of children receiving nebulised adrenaline and in 25% of children receiving placebo. No steroids were used. They posited that it is not likely that the phenomenon is related to adrenaline only, but rather to ongoing inflammation and oedema in the airway. They concluded that nebulised adrenaline is effective for the treatment of acute mild to moderately severe croup and that it should be used as a first line treatment [14]. This has not been taken up universally, but it is now standard practice in some countries to use steroids and nebulised adrenaline in the emergency department, watch the patients for 2 h and then discharge home if well enough [2]. The final two studies both used steroids and nebulised adrenaline, showing clearly a good response to the treatment with no rebound or indeed any major re-emergence of symptoms [12, 13].

The data presented here are reassuring in that re-emergence of symptoms may occur but is no worse than baseline. The re-emergence of symptoms is less marked in studies when children received concurrent steroids.

So, in answer to the proposed question: "Do children with croup (patient group) when treated with nebulised adrenaline (intervention) develop re-emergence of stridor, worse than initial baseline presentation (comparison) as defined by changes in symptoms score (outcome)?" Or "Rebound stridor in children with croup after nebulised adrenaline: does it really exist?" The answer is no.

Key points

- Children with croup who are treated with nebulised adrenaline may develop re-emergence of symptoms, but they are not worse than baseline. They do not have rebound phenomenon.
- The re-emergence of symptoms after treatment with nebulised adrenaline is less pronounced in children who had concurrent treatment with oral or parenteral glucocorticoids. Hence children who have had moderate to severe croup receiving nebulised adrenaline should be given oral or parenteral glucocorticoids.

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Conflict of interest

None declared.

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