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A Risk-Benefit Assessment of Corticosteroids in the Management of Croup

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Summary

Croup is an acute clinical syndrome of childhood characterised by a barking cough, hoarse voice, stridor and a variable degree of respiratory distress. A meta-analysis and subsequent controlled trials clearly demonstrate that corticosteroids are efficacious in the management of croup, with their benefits conclusively outweighing their risks. In mild to moderate cases of croup either systemic or nebulised corticosteroids decrease symptoms and need for hospitalisation. Most reports use IM dexamethasone 0.6 mg/kg, although it is likely that dexamethasone 0.15 mg/kg has a similar effect. In controlled studies nebulised budesonide 2mg is superior to placebo, and appears to have equivalent efficacy to oral dexamethasone. The risk of a single or short course of systemic corticosteroids are minimal, the only potential significant adverse effect being increased risk of severe varicella infection. Short courses of nebulised budesonide have no major adverse effects, and thus are likely to cause fewer adverse effects than systemic corticosteroids, although this is as yet unproven. On the body of data published to date, either oral dexamethasone 0.15 mg/kg or nebulised budesonide 2mg are effective for mild to moderate croup. In severe croup requiring intubation, oral prednisolone 1 mg/kg every 12 hours decreases the duration of intubation and the need for re intubation. Unless there are clear contraindications, corticosteroids are the treatment of choice in mild, moderate and severe croup.

Croup is an acute clinical syndrome of childhood characterised by a barking cough, hoarse voice, stridor and a variable degree of respiratory distress. Symptoms of an upper respiratory tract infection may be present for a day or two prior to onset. Characteristically the symptoms of croup are worse at night – often the presentation is the child (and parents) being woken by respiratory distress. The aetiology is viral, most commonly a parainfluenza virus, with parainfluenza virus type I accounting for half of identified cases. Other causes include influenza virus, respiratory syncytial virus and *Mycoplasma pneumoniae*.[1]

A community study conducted in the 1960s to 1970s in the US reported an incidence of croup of 1.8% of children, with the peak incidence between 1 and 2 years of age. The incidence in boys was 1.5 times greater than in girls and 1% of all cases required hospitalisation.[1] In a recent study in the UK, the hospitalisation rate was 0.2% per year for all children less than 14 years of age, with mean age for hospitalisation of 32 months and an age range of 3 months to 9 years.[2] Two percent of hospitalised children will need intubation and mechanical ventilation, although this rate is likely to have fallen with the wider use of corticosteroids in the management of croup.[3]

Croup must be distinguished from potentially life-threatening conditions that may present in children with stridor such as epiglottitis, bacterial tracheitis and inhalation of a foreign body. Epiglottitis caused by *Haemophilus influenzae* type b is the most important differential diagnosis because of the high risk of rapid airway obstruction and death, although the incidence of epiglottitis has decreased significantly with the introduction of *H. influenzae* immunisation.

Although community data are scarce, it is likely that the majority of patients with croup do not seek medical advice. Of those who do, most only require accurate assessment, gentle handling and general supportive measures.[4] Mist or steam treatment is frequently recommended and parents are encouraged to keep the child in a steam filled bathroom. However, despite anecdotal reports there is no hard evidence of the benefits of steam treatment,[5] and potential adverse effects include scalding of the child due to steaming hot water.

Management in hospital includes the use of nebulised L- or racemic epinephrine (adrenaline). Although clearly effective, the action of epinephrine is short-lived, and there is a rebound effect.[6] There is extensive evidence for the beneficial effect of systemic corticosteroids in croup. A recent development has been the recognition that nebulised corticosteroids are also efficacious in the treatment of croup.

For the purposes of this risk-benefit assessment, we performed computer literature searches on several electronic medical databases from 1960 to the present day. Further studies were revealed using author searches from seminal papers, conference abstracts and from citations. Relevant English language publications were identified including case reports of the complications of steroid use.

1. Systemic Corticosteroids in the Management of Moderate to Severe Croup

The evidence for the efficacy of corticosteroids in the management of croup is stronger now than at any time in the past 20 years. Corticosteroids are now more commonly used in the initial management of patients requiring hospitalisation for croup,[3] and many authors recommend that intramuscular or intravenous dexamethasone 0.6 mg/kg be given in the emergency room to those patients with viral croup requiring hospital admission.[7]

Early studies were unsatisfactory with small numbers of randomised patients and had insufficient statistical power to distinguish small but meaningful benefits of systemic corticosteroids. In 1989, Kairys et al.[8] performed a meta-analysis of 9 methodologically sound randomised controlled trials[9-17] including some 1126 patients. Clinical improvement 12 and 24 hours after treatment was evaluated, as was the need for endotracheal intubation. This analysis indicated that the use of corticosteroids in children hospitalised with croup was associated with a greater proportion of children

whose symptoms were improved at 12 hours [odds ratio (OR) = 2.25, 95% confidence interval (CI) = 1.66 to 3.06] and 24 hours (OR = 3.19, 95% CI = 1.70 to 5.99) and a reduced incidence of intubation (OR = 0.21, 95% CI = 0.05 to 0.84). Higher initial doses of corticosteroids, i.e. cortisone at dosage of more than 125mg or hydrocortisone at dosage of more than 100mg, were associated with a greater proportion of children whose symptoms had improved at 12 hours. This study supported the use of corticosteroids in the management of croup for the hospitalised child.

Subsequent studies have reinforced the beneficial effect reported by Kairys and colleagues. Super et al.[18] in a randomised controlled trial of 29 children hospitalised for croup reported that a single injection of intramuscular dexamethasone (0.6 mg/kg) resulted in significant improvements in croup score compared to saline placebo. 12 hours after treatment the children who received dexamethasone had a statistically significant decline in median croup score from 4.5 to 1.0 ($p < 0.001$), whereas the patients receiving the placebo did not. By 24 hours, 85% of the children who received dexamethasone had a decrease of 2 or more points in the croup score group compared with 33% of the children who received placebo ($p = 0.027$). During this same period, only 19% of patients receiving dexamethasone required 2 or more racemic epinephrine treatments compared with 62% of patients who received the placebo ($p < 0.05$).

In addition, there is accumulating evidence for the use of systemic corticosteroids in patients with milder disease who are able to be managed as outpatients. Cruz et al.[19] reported a randomised comparison of intramuscular dexamethasone 0.6 mg/kg or saline placebo in the outpatient management of croup in 38 children aged 6 months to 5 years. Severity of illness was significantly decreased in 84% of the dexamethasone-treated children within 24 hours after treatment compared with 42% of the placebo-treated children ($p = 0.03$). Four placebo-treated children sought medical attention in the subsequent 48 hours compared with 1 of the dexamethasone-treated children, although none required hospitalisation. It is likely that a lower dose of dexamethasone would have been sufficient, as Geelhoed and colleagues have demonstrated similar efficacy for oral dexamethasone at doses of 0.15 mg/kg, 0.3 mg/kg and 0.6 mg/kg in children with mild croup.[20] They have since reported a randomised comparison of a single dose of oral dexamethasone 0.15 mg/kg and placebo in 100 children aged 4 months to 10 years attending an emergency department for mild croup.[21] None of the children who received dexamethasone required further medical attention compared with 8 of the children who received placebo.

2. Systemic Corticosteroids in the Management of Patients with Croup Who Require Intubation

Croup requiring intubation is clearly at the severe end of the spectrum, and intubation and mechanical ventilation even in the most experienced centres is not without risk. Researchers who conducted a retrospective analysis of 2623 children with croup who were admitted to the Royal Children's Hospital, Melbourne, Australia, reported that 416 patients (16%) were admitted to the intensive care unit, of whom 176 required intubation. Of the intubated children, 117 patients were successfully extubated at the first attempt and 59 needed reintubation. Of the patients who were reintubated, 35 were given corticosteroids prior to subsequent extubation attempts. Only 1 patient who had received corticosteroids failed extubation, while 59% of those who did not receive corticosteroids required reintubation.[22]

The same unit has subsequently clearly demonstrated the efficacy of oral corticosteroids for children intubated because of severe croup.[23] In a prospective placebo-controlled study Tibballs et al.[23] investigated the effect of 1 mg/kg prednisolone every 12 hours by nasogastric tube until 24 hours after extubation on the duration of intubation and the need for reintubation. Children under 6 months or those with congenital airway anomalies or previous intubations were excluded. Only 2 (5%) of the prednisolone-treated children required reintubation

after accidental or elective extubation compared with 11 (34%) of the placebo-treated children ($p = 0.004$). Survival analysis with log-normal regression showed that the duration of intubation was shorter with corticosteroid therapy ($p < 0.003$) and increasing age ($p < 0.02$). The median duration of intubation was 138 hours (95% CI = 118 to 160) in children who received placebo compared with 98 hours (95% CI = 85 to 113) in the prednisolone group.

3. Risks of Short Term Systemic Corticosteroid Therapy

Compared with cortisol, the synthetic corticosteroids such as prednisone, prednisolone or betamethasone have more potent anti-inflammatory activity, a reduced mineralocorticoid effect and a longer biological half life. In school age children as little as 5mg of prednisolone per day for 2 weeks can result in impaired short-term growth.[24] The documented adverse effects of oral corticosteroids in childhood include adrenal suppression,[25] decreased bone mineralisation[26] and cataracts.[27] However, the evidence for a significant effect on any of the above due to short term use of systemic corticosteroids is scant.

Use of systemic corticosteroids has been associated with severe varicella. In a case-control study, Dowell and Bresee[28] compared corticosteroid exposure in 35 children with severe varicella and 10 000 control individuals. 26% of the children with severe varicella had received corticosteroids within 30 days prior to the onset of their rash compared with 20 (0.2%) of the control individuals (OR = 178, 95% CI = 59 to 541). Of the 13 patients with severe varicella whose dosage was recorded, 7 had received less than the equivalent of 2 mg/kg per day of prednisone. The timing of the corticosteroid use in those who had severe varicella clustered within the incubation period for the virus. Thus, in this study systemic corticosteroids substantially increased the risk of severe or fatal varicella.

Potential local adverse effects of intramuscular corticosteroids include subcutaneous atrophy[29] in adults. Although the condition is often reversible, instances of long term disfigurement are well documented.

4. Inhaled Corticosteroids in Croup

Inhaled or nebulised corticosteroids appear an attractive alternative to systemic corticosteroids in the treatment of airway disorders. The corticosteroids are delivered directly to the site of inflammation, thus it is possible to reduce the dose required and potentially to decrease treatment-associated adverse effects. Inhaled corticosteroids via a meter dose inhaler are well established in the treatment of childhood asthma, resulting in a decrease in adverse effects compared with oral corticosteroids.[30]

All reports to date on the use of inhaled corticosteroids in croup have used nebulised budesonide. Use of nebulised corticosteroids results in decreased dose of oral corticosteroids in pre-school children with corticosteroid-dependent viral asthma and viral-associated wheezing.[31] However, unlike inhaled corticosteroids via a meter dose inhaler, there are no head-to-head comparisons between the adverse effects of nebulised and systemic corticosteroids in croup or in any respiratory indication. Thus, although theoretically attractive, there is no direct evidence of a decrease in adverse effects with nebulised corticosteroids compared with systemic corticosteroids.

There is a large variation in the performance characteristics of nebulisers in terms of particle size and aerosol output,[32] and the efficacy of nebulised budesonide in croup could be influenced by the type of nebuliser used. As little as 10% of the administered dose of nebulised budesonide is actually inhaled by the infant.[33] Unlike diseases involving the small airways, such as asthma, where it is desirable for a nebuliser to generate respirable particles ($< 5\mu m$), it is possible that the generation of larger particles, which are more likely to be deposited in the upper airway, is desirable in the treatment of croup. As the systemic bioavailability of inhaled corticosteroids is dependent on the proportion deposited in the intra-pulmonary airways,[34]

Table I. Controlled trials of inhaled corticosteroids in the management of croup

Reference	Protocol	Comparison	Nebuliser	No. of patients	Outcome	Result
Husby et al.[36]	r, db, pc	PLA *vs* BUD 1mg x 2	'Parinebuliser CR 60' 8 L/min	36	Croup score and clinical impression after 2h	BUD > PLA
Klassen et al.[37]	r, db, pc	PLA *vs* BUD 2mg	'Updraft' 6 L/min	54	2 point decrease in croup score at 4h	BUD > PLA
					Discharge from emergency room[a]	BUD > PLA
Fitzgerald et al.[38]	r, db, pc	EPI 4mg *vs* BUD 2mg	N/A	66	Croup scores 0.5 to 24h after hospitalisation	BUD ≡ EPI
Geelhoed & MacDonald[39]	r, db, ddc	PLA *vs* DEX 0.6mg/kg *vs* BUD 2mg	Airflow® mask 8 L/min	80	Time to croup score <2	BUD ≡ DEX > PLA
					Duration of hospitalisation	BUD ≡ DEX > PLA
					Time to use of epinephrine nebuliser <1h	BUD ≡ DEX > PLA
Klassen et al.[40]	r, db, pc	DEX plus BUD 2mg or PLA	'Updraft' 5-6 L/min	50	2 point decrease in croup score at 4h	BUD > PLA

a Not *a priori* outcome measure.

Abbreviations and symbols: BUD = budesonide; db = double-blind; ddc = double dummy controlled; DEX = dexamethasone; EPI = epinephrine (adrenaline); N/A = not applicable; pc = placebo-controlled; PLA = placebo; r = randomised; > = greater effect; ≡ = equivalent effect.

so the generation of smaller particles would theoretically result in decreased upper airway deposition (leading to decreased efficacy) and increased systemic bioavailability (leading to increased adverse effects). However, in practice it is unlikely that the type of nebuliser is of paramount importance.

A potential weakness in the interpretation of intervention studies of nebulised corticosteroids in the management of croup is the lack of objective measures of severity. Oxygen saturation is a poor marker of severity.[35] Consequently changes in croup score, based on pre-determined clinical findings, are used as study endpoints. Most studies are in mild to moderate croup[36-40] using a Westley-type score where the combination of stridor (0 to 2), retraction (0 to 3), air entry (0 to 2), cyanosis (0 to 5) and conscious state (0 to 5) to gives a total score of 17, with loading of the score towards cyanosis and conscious state at the more severe end.[41] Croup scores are used as inclusion criteria, and as outcome measures. The entry severity of cases has differed from a score of 3[37] through to 6.[36,38] Although the reported interobserver repeatability of croup scores is excellent in milder cases,[36,40] it is worth noting that the only published validation of croup scores was for need for admission to an intensive care unit.[2] To date there are 4 published studies plus 1 in abstract form of nebulised budesonide in croup (see table 1)[36-40] – either placebo-controlled studies or comparisons with oral dexamethasone or nebulised epinephrine.

4.1 Placebo-Controlled Studies

There are 2 published placebo-controlled studies of nebulised budesonide in croup. Husby et al.[36] reported the effect of 2 doses of 1mg budesonide 30 minutes apart or saline placebo in 36 infants and children aged 5 months to 5 years hospitalised for croup. A modified Westley score was used based on stridor, cough, retractions, dyspnoea and cyanosis, and entry criteria was an initial croup score of 6 or more. In addition the overall clinical impression was evaluated (0 to 100). Two hours after treatment, the croup score in the budesonide treated group had decreased from 8 to 4.5, while the croup score in the placebo group remained unchanged at 8 ($p < 0.01$). The overall

clinicalimpressionassessment score decreased in the budesonide-treated group from 50 to 25, whereas it remained constant in the placebo group ($p < 0.01$). When the individual symptoms of the croup score were compared, only cough and stridor were significantly decreased, there being no significant differences in retractions, dyspnoea, or cyanosis.

Klassen et al.[37] reported the effect of a single 2mg dose of budesonide or saline placebo on 54 children aged 3 months to 5 years attending an emergency room for croup. The entry criteria was a Westley score of 2 to 7 out of a possible 17 and the *a priori* end-point was the proportion of children showing a 2 point decrease in croup score within 4 hours. The median croup score at entry into the study was 4 in both groups. After 4 hours the median croup score was significantly lower in the budesonide-treated children than in the placebo-treated children (1 v 3, $p = 0.005$). In addition the budesonide-treated children were discharged from the emergency department significantly earlier than the placebo-treated children (Kaplan-Meier $p = 0.002$). One week after enrolment, 21 of 27 children who received placebo had required dexamethasone treatment, as compared with 15 of 27 children who received budesonide ($p = 0.10$), and 7 patients who received placebo had been hospitalised, compared with 1 patient who received budesonide ($p = 0.05$).

4.2 Comparison with Epinephrine (Adrenaline)

There is only 1 published comparison of budesonide and epinephrine in croup and this is only available as an abstract. Fitzgerald et al.[38] compared the effect of a single 2mg dose of nebulised budesonide with a single 4mg dose of adrenaline in 66 children aged 6 months to 6 years. The entry criteria were a Husby croup score (see section 4.1) of 6 or above, and croup scores were periodically assessed over a 24 hour period. The study was designed to detect a 2 point difference between treatments with 95% power. All the children responded to treatment and there was no significant difference in croup score between the budesonide- and epinephrine-treated children at any of the assessments.

4.3 Controlled Comparisons with Dexamethasone

There are 2 published studies of budesonide with dexamethasone – one where budesonide is directly compared with oral dexamethasone or placebo,[39] and another where budesonide and placebo are compared in addition to oral dexamethasone.[40] Geelhoed and MacDonald[39] compared the effects of a single dose of oral dexamethasone 0.6 mg/kg with a single 2mg dose of nebulised budesonide or placebo in a double-blind, double-dummy study of 80 children aged 5 months to 15 years attending an emergency department with croup.

There was no significant difference in median duration of hospitalisation between the dexamethasone- and budesonide-treated children (12 and 13 hours, respectively), but median duration of hospitalisation was significantly shorter for both than placebo (20 hours, $p < 0.03$). Similarly, croup scores were not significantly different between the dexamethasone- and budesonide-treated children at any time, while both groups achieved croup scores of 1 or less in a shorter period (2 and 3 hours, respectively) than the placebo group (8 hours, $p < 0.01$). Furthermore, 6 of the 30 placebo-treated children (20%) required nebulised epinephrine after the first hour compared with none of the corticosteroid-treated children ($p < 0.02$).

In comparison, Klassen et al.[40] compared the addition of a single 2mg dose of nebulised budesonide or placebo to the effect of a single dose of oral dexamethasone 0.6 mg/kg in 50 children aged 3 months to 5 years attending an emergency department for croup. As in their previous study,[37] the entry criteria was a Westley score of 2 to 7 out of a possible 17, and again the *a priori* end-point was the proportion of children showing a 2 point decrease in croup score within 4 hours. There was a significant difference between the budesonide- and placebo-treated children, with 21 (84%) of the

budesonide-treated children showing a 2 point decrease in croup score within 4 hours compared with 14 (56%) of the placebo-treated children ($p < 0.03$). They estimated that after treatment with oral dexamethasone, 4 patients with mild to moderate croup would need to be treated with nebulised budesonide for one patient to have a 2 point improvement in croup score. However, there was no significant difference in subsequent doses of dexamethasone or hospitalisation rate between the budesonide- and placebo-treated children.

5. Risks Associated with Inhaled Corticosteroids in Croup

Budesonide has a short plasma half-life of approximately 3 hours in adults.[34] There is extensive first-pass metabolism with only 10% of an orally administered dose reaching the systemic circulation.[34] Although the data are scanty, nebulised budesonide appears to confer no significant risks to children in general. No adverse effects were detected in any of the published studies[35,37,39,40] and no conclusions can be drawn on potential adverse effects from the Fitzgerald abstract.[38] The only potentially adverse effect was that 3 of the 50 children vomited their dexamethasone within 30 minutes in the study reported by Klassen and colleagues.[40]

It is difficult to assess the potential adverse effects of long term nebulised budesonide due to the paucity of published studies in children. Ilangovan et al.[31] reported that regular nebulised budesonide significantly reduced the requirement for treatment with oral corticosteroids in a controlled study of 36 pre-school children with severe asthma, with no significant adverse effects. Although inhaled budesonide via a meter dose inhaler appears to have an admirable safety profile,[34] the significant differences in drug delivery and dose preclude direct comparison.

6. Conclusions

Controlled trials demonstrate that corticosteroids are of clear benefit in the management of croup, with their benefits conclusively outweighing their risks. The risks associated with a single dose or a short course of systemic corticosteroids are minimal, the only potential significant adverse effect being an increased risk of severe varicella infection if corticosteroids are administered at the time of exposure.

For patients with severe croup, oral corticosteroids decrease the duration of intubation and decrease the need for reintubation. In patients with less severe croup, corticosteroids decrease symptoms and need for hospitalisation. There appear no significant differences in therapeutic effect between systemic and nebulised corticosteroids, although there is preliminary evidence that use of both concurrently may be of benefit in the short term. Nebulised corticosteroids are considerably more expensive than systemic corticosteroids and require specialist equipment, but are less painful to administer than an intramuscular injection. It is likely that nebulised corticosteroids have fewer adverse effects that systemic corticosteroids, although this assertion is still unproven.

From the body of data published to date, it appears that either oral dexamethasone 0.15 mg/kg or nebulised budesonide 2mg are effective for mild to moderate croup, while oral prednisolone 1 mg/kg every 12 hours is effective for croup requiring intubation. Unless there are clear contraindications, corticosteroids are the treatment of choice in mild to moderate, and severe croup.

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