

The Use and Abuse of Steroids in Perinatal Medicine

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Abstract

Corticosteroids are one of the most powerful drugs increasingly used in the perinatal and neonatal period. This review discusses the merits and demerits of antenatal as well as postnatal use of steroids. A single course of antenatal corticosteroids in women at risk of premature delivery is highly effective in reducing respiratory distress syndrome (RDS), intraventricular haemorrhage and neonatal mortality and also neurodevelopmental sequelae including cerebral palsy. However, there is less evidence to support the practice of multiple courses of corticosteroids, with some animal and retrospective human studies suggesting an association with neurological impairment and reduction in birth weight as well as lung weight. Postnatal systemic corticosteroids have shown benefits in reducing chronic lung disease and improving survival for infants. However, besides short-term adverse effects, the follow-up studies have raised concern that they may increase the risk of neurodevelopmental disability, particularly cerebral palsy in survivors. Systemic corticosteroids may have a role in infants who had repeated and prolonged intubations and those with pressor-resistant hypotension. Alternative strategies for prevention of chronic lung disease, such as inhaled steroids, methylprednisolone and hydrocortisone, may need further studies with larger sample sizes. Data from animal research have revealed that fetal glucocorticoid exposure may have a role in programming the individual to adult degenerative diseases. Based on the current evidence, it is recommended that women at risk of preterm delivery receive a single course of glucocorticoids. Randomised controlled trials are needed to establish the true effects of multiple courses of antenatal corticosteroids. More research is also needed to study the long-term neurodevelopmental outcome of both multiple courses of antenatal corticosteroids, as well as postnatal corticosteroid therapy.

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Introduction

Preterm birth, delivery prior to 37 weeks of gestational age, accounts for a major and disproportionate amount of infant and neonatal morbidity and mortality. Despite advances in medical technology, the prevalence of preterm birth in Singapore has increased, secondary to an increase in multiple gestations and obstetric interventions.¹ In KK Women's and Children's Hospital (KKH), Singapore, a total of 11.1% of 15,025 births in 2002 were preterm (prior to 37 completed weeks) and 2.5% of these 15,025 births were less than 34 completed weeks of gestation. However, improvements have been made in regards to preterm neonatal morbidity and mortality, due to the increased use of antenatal corticosteroids (ACS) prior to preterm delivery.²

Physiology and Pharmacology

Alveolar type II pneumocytes synthesize and secrete pulmonary surfactant, which maintains alveolar stability and normal lung function. Its deficiency in the newborn

often leads to respiratory distress syndrome (RDS). Corticosteroids are known to accelerate maturation of developmentally regulated proteins and to stimulate cytodifferentiation in numerous cells, including type II pneumocytes. They increase the production of surfactant, increase lung compliance and maximal lung volume. Corticosteroid treatment also appears to reduce protein leak from the pulmonary vasculature into the airspace and appears to accelerate clearance of lung liquid prior to delivery. These effects are essential in the transition to air breathing.

The preferred ACS are dexamethasone and betamethasone (with dexamethasone more commonly used in Singapore). The American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice³ recommends that betamethasone (12 mg) be given intramuscularly every 24 hours for 2 doses or dexamethasone (6 mg) be given intramuscularly every 12 hours for 4 doses. The Singapore Ministry of Health (MOH) guidelines⁴

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recommend that maternal corticosteroid be administered using 2 doses of 12 mg of betamethasone/dexamethasone intramuscularly 12 to 24 hours apart.

These corticosteroids readily cross the placenta in their biologically active forms. They are weak in immuno-suppressive activity, devoid of mineralocorticoid activity and have a longer duration of action than cortisol. The bioavailability of corticosteroids to the fetus is reduced secondary to placental metabolism. The umbilical vein concentrations of betamethasone are approximately 25% to 30% of maternal venous concentrations. However, corticosteroids do not remain in the fetal circulation for long. In one study, when the levels of betamethasone administered prior to birth were assayed in cord blood, the drug was undetectable 40 hours following the injection.

Use of Antenatal Steroids

ACS were first used to enhance fetal lung maturation since the seminal work of Liggins and Howie in 1972.⁵ However, its use to reduce neonatal RDS in preterm delivery only became routine practice in late 1990s. In 1990, Crowley first summarised as an evidence-based systematic review, the results of 12 randomised controlled trials (RCTs) which demonstrated that ACS were highly effective in reducing rates of RDS and neonatal mortality.⁶ This led to the worldwide recognition of the use of ACS. Four years later, the National Institutes of Health (NIH) held a consensus conference and summarised the benefits of a single course of ACS in women (24 to 34 weeks' gestation) at increased risk for preterm birth. Widespread prescribing of corticosteroids only became the norm in the USA following this NIH Consensus declaration in 1994 that 'antenatal corticosteroid therapy is indicated in women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality as well as substantial savings in health care costs'.⁷ In fact, the late routine usage of ACS from the 1990s despite good evidence since the late 1970s has been one of the major lost opportunities in perinatal medicine worldwide, where many neonatal deaths and morbidities could have been decreased or prevented for 2 decades. This highlighted the need and gave impetus for evidence-based systematic review and effective dissemination worldwide.

Benefits and Risks of Single-course Antenatal Corticosteroids

The greatest benefit of a single course of ACS for fetuses at increased risk of preterm birth is a reduction in RDS. The Cochrane Database of Systematic Reviews assessed 18 trials involving a total of 3700 babies.⁸ It was concluded that antenatal steroids were associated with a significant reduction in RDS [odds ratio (OR), 0.51; 95% confidence interval (CI), 0.42-0.61], overall mortality (OR, 0.60; 95%

CI, 0.48-0.76), intraventricular haemorrhage, the need for surfactant therapy and a variety of other adverse outcomes. A large follow-up study of very-low-birth-weight (VLBW) infants has confirmed these findings⁹ and another has shown the dramatic effect on increased chances of intact survival.² Infants exposed to ACS have also been found to have an improved circulatory stability, requiring reduced amounts of oxygen and ventilatory support. A non-randomised study reported high incidence of cystic periventricular leukomalacia (PVL) in infants born to mothers who are treated with dexamethasone compared to betamethasone (11% vs 4.4%) but this adverse effect was attributed to the presence of sulphites in certain preparation of dexamethasone.¹⁰

Follow-up studies of infants enrolled in RCTs have not demonstrated any long-term adverse effects following a single course of ACS.¹¹⁻¹⁴ There were no significant differences between children that received a single course of ACS as compared to those who did not, in terms of growth, intelligence, pulmonary function, motor development, scholastic achievement or sexual orientation.^{12,14} Pooling of the data from 4 trials which reported neurodevelopmental follow-up revealed significant reduction in cerebral palsy (OR, 0.59; CI, 0.35-0.97) in infants of mothers who had received ACS.¹⁵ Doyle et al¹⁶ have reported a significantly higher IQ in 14-year-old teenagers exposed to ACS.

The potential adverse maternal side effects of a single course of ACS include an increased risk of infection such as chorioamnionitis and endometritis. However, in Crowley's meta-analysis, the frequency of maternal infection was similar between women who received and those who did not receive ACS; although, in one small study of 42 women, the rate of maternal infection was increased among women who received ACS with preterm premature rupture of membranes (PPROM) >24 hours.⁸ It is widely accepted that a single course of ACS reduces morbidity and mortality in preterm infants and is indicated for most women at increased risk of preterm birth prior to 34 weeks' gestation. The efficacy of this policy is now well established and has gone on to become one of the foremost examples of evidence-based medicine improving clinical outcome.

Effects of a Single Course of Antenatal Steroids for Women who Remain Undelivered After 1 Week

A large proportion of women presenting with threatened preterm labour, or other conditions requiring antenatal steroids, will not have delivered within 7 days. Although the effectiveness of one course of ACS (greater benefit than risk for those treated) has been proven, there is uncertainty as to how long the treatment should continue to be effective

if the woman remains undelivered 7 or more days following the initial dose.

Liggins trial⁵ in 1972 showed that the risk of RDS was significantly reduced following treatment with ACS (vs control) among fetuses born between 2 days and less than 7 days following trial entry (3.6% vs 33.3%, $P = 0.03$), but the effect on RDS was not statistically significant following treatment with ACS (vs control) if fetuses were born 7 or more days following trial entry (2.2% vs 9.4%, $P > 0.05$). The Collaborative Group on Antenatal Steroid Therapy¹⁷ reported that ACS reduced the risk of RDS, if delivery occurred 24 hours to 7 days following trial entry (9.3% vs 20.1%), and if delivery occurred >7 days following trial entry, the reduction was of a smaller magnitude (6.0% vs 10.5%). Despite the possibility that the effectiveness of a single course of ACS may be lost if the woman remains undelivered 7 or more days following the initial dose, the Cochrane meta-analysis by Crowley⁸ showed a reduction in RDS for these fetuses ($n = 265$) (OR 0.41), albeit of only borderline statistical significance (95% CI, 0.18–0.98), and this OR is actually of a similar magnitude to that for fetuses born between 24 hours and 7 days following the initial dose ($n = 728$) (OR, 0.38; 95% CI, 0.25–0.57). However, because fewer mothers and fetuses delivering 7 or more days following the initial dose were included in this meta-analysis, and because the overall risk of RDS for those infants born later was lower, the 95% CI about the OR is wide. Therefore, it is possible that the beneficial effects of a single course of ACS continue beyond 7 days.⁸

Multiple-course Prescribing

There is no clear evidence on the practice of repeated courses of steroids for the same indication currently. However, this has not prevented it from becoming routine in many centres managing cases where the threat of premature delivery remains, as the risk of RDS and other complications of prematurity are high for fetuses born very preterm. Some clinicians have suggested that weekly courses of ACS should be given to women who are at increased risk of preterm birth (e.g. in multiple pregnancy) and remain undelivered 7 or more days following the initial dose. In some overseas and local centres, this approach unfortunately became routine despite the fact that multiple courses of ACS have not been evaluated in well-designed RCTs and the benefit-to-risk ratio is not clear. A study of US obstetricians by Planer et al¹⁸ in 1995 showed an overwhelming urge to prescribe repeated courses of antenatal steroids, which continued even when the women were deemed not to be at risk. In those perceived to be at continued risk of preterm delivery, 92% of obstetricians in that study would repeat steroids on a weekly basis. In a 1996 study,¹⁹ which involved a randomised trial of inpatient

versus outpatient management of placenta praevia, it was reported that both groups received weekly corticosteroids until 32 weeks' gestation. In a survey of Australian obstetricians published in 1998, 50% to 85% of obstetricians indicated that they prescribed multiple courses of ACS for women who remained at increased risk of preterm birth.²⁰ A postal questionnaire of 279 obstetric units in the UK in 1999 revealed that 98% of the 75% responding would prescribe repeated doses of antenatal corticosteroids, with the major indications being PROM (84%) and suspected term labour (82%).²¹

Multiple Courses of ACS: Evidence from RCTs

Currently, there appeared to be only one RCT (by Guinn et al²²) which compared single versus multiple course of ACS. This RCT of 502 women between 24 and 32 completed weeks who were at high of preterm delivery, revealed no difference in the primary outcome (a composite of RDS, BPD, neonatal sepsis, necrotising enterocolitis or neonatal death) between infants who received single versus multiple courses of ACS (28.0% vs 22.5%, $P = 0.16$). However, this trial was stopped early before reaching its planned sample size and thus lacked power for finding clinically important reductions in adverse perinatal outcomes. Despite its early closure, subgroup analyses revealed significant decreases in composite morbidity among neonates delivered prior to 28 weeks' gestation and in severe RDS. Another RCT ($n = 146$) by Papageorgiou et al²³ comparing multiple courses of ACS (betamethasone) versus placebo showed that ACS was associated with a statistically significant reduction in RDS and death, but more than half of the randomised fetuses were excluded from the analysis, and the effect found may have been the result of the initial versus the subsequent courses. There was also a significantly higher incidence of hypoglycaemia among infants in the betamethasone group.

Multiple Courses of ACS: Retrospective and Animal Data

Elimian et al²⁴ in a retrospective study showed that multiple courses of antenatal steroids reduced significantly the incidence of RDS with no apparent increase in neonatal sepsis or disturbances in fetal growth. Another retrospective study by Pratt et al²⁵ showed a significant decrease in oxygen use in infants who received multiple courses of ACS. A 3-year follow-up study of children who received single versus multiple courses of ACS showed no difference in growth or disabilities between the two groups.²⁶ Another longer follow-up study by Rotmensch et al²⁷ reported no adverse effects on blood pressure or growth. Studies in animals have found progressive improvement in postnatal lung function following multiple courses of ACS.^{28,29}

Multiple Courses of ACS: Adverse Effects

However, adverse effects of multiple courses of ACS have also been presented.³⁰ They are summarised below.

Intrauterine Growth Restriction

Assessment of neonates exposed to multiple doses of steroids has not been reassuring. French et al²⁶ revealed an indirect relationship between increasing numbers of corticosteroid courses and birth weight ratios. A birth weight reduction of up to 9% and a decrease in head circumference of 4% was noted. Banks et al³¹ confirmed the same detrimental effect on growth. Abbasi et al³² also showed exposure to multiple courses of antenatal corticosteroids compared with a single course, was associated with a reduction in birth head circumference.

Adverse Pulmonary Effects

Banks et al³³ showed that multiple courses of antenatal corticosteroids are associated with early severe lung disease in preterm neonates. Stewart et al³⁴ studied the effects of multiple dosing on lung maturation in animal studies and showed advanced breathing patterns and alveolar development in the offspring of mice treated with multiple doses. This was associated with a reduction in lung weight, which continued into adulthood.

Adverse Neurological Effects

Several animal studies have suggested an adverse effect on fetal neurological development. Administration of both single and multiple courses of corticosteroids have been shown to cause growth retardation of the fetal brain in sheep.³⁵ Alterations to the process of myelination of the developing rat brain³⁶ and of the hippocampus in rhesus monkeys have been reported.³⁷ In the latter, induced by treatment with dexamethasone, the changes were dose-dependent and more severe with multiple doses. Evidence of a significant delay in the myelination of the optic nerve axons of sheep following repeated steroid doses has been reported.³⁸

Adverse Endocrine Effects

Adverse effects reported included a case of neonatal cushingoid syndrome following 7 courses of ACS.³⁹ In animal models, multiple courses of ACS had been associated with elevated basal plasma corticosterone levels and hypertension.^{40,41} In addition, multiple courses of ACS had been associated with permanent changes in the expression of glucocorticoid receptors in the hippocampus and limbic system in animal studies, suggestive of a decrease in central glucocorticoid feedback.^{42,43}

Neonatal Mortality

Banks et al,³¹ in a retrospective analysis of 710 neonates

born between 25 and 32 weeks of gestation, showed that multiple (3 or more) courses of ACS was associated with increased mortality in neonates after controlling for gestation (adjusted OR, 2.8; 95% CI, 1.3-5.9; $P = 0.01$).

Currently, there is a paucity of RCTs in this area and work on humans has been mostly retrospective and uncontrolled. Aghajafari et al⁴⁴ performed a systematic review and meta-analysis on multiple courses versus single course of antenatal corticosteroids in 2001 and reported that it was impossible to establish the true effects of multiple courses of antenatal corticosteroids by the review of the results of observational studies because of the effects of confounding variables. RCTs are needed to address this important issue. There is fresh impetus for prospective, multicentre randomised trials. Trials include MACS (Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study) coordinated by the Centre for Research in Women's Health from Toronto since 2001 and TEAMS (Trial of the Effects of Antenatal Multiple Courses of Steroids versus a Single Course) coordinated by National Perinatal Epidemiology Unit in Oxford since 1999.

Glucocorticoids in Fetuses with Congenital Adrenal Hyperplasia (CAH)

Glucocorticoids has also been used to treat fetuses at risk of CAH and this has been shown to be effective in inhibiting or reducing virilisation of affected female fetuses.⁴⁵ Since CAH is inherited as an autosomal recessive disorder and only affected girls benefit from the treatment, 7 out of 8 fetuses are treated unnecessarily. Moreover, for the treatment to be effective, dexamethasone should be started as early as 6 to 7 weeks of pregnancy and continued until delivery. The safety of this method of treatment needs to be considered in the light of the long-term side effects of antenatal glucocorticoids as discussed earlier.

Glucocorticoid-programming of the Hypothalamic-pituitary-adrenal (HPA) Function

Numerous epidemiological studies suggest that factors operating early in life permanently alter the structure and physiology of the adult offspring through 'fetal programming'.⁴⁶ It has been shown in animal models that antenatal exposure to endogenous or exogenous glucocorticoids reduces offspring birth weight and produces permanent hypertension, hyperglycaemia, hyperinsulinaemia, altered behaviour and neuroendocrine responses throughout the lifespan.^{40-43,47} The mechanism underlying fetal programming includes determination of the 'set-point' of the HPA axis and of tissue glucocorticoid receptor expression.⁴⁷ The long-term effects of fetal dexamethasone in humans are unclear and whether it has a role in programming the individual to adult degenerative diseases remains to be studied.

Postnatal Systemic Corticosteroids for Chronic Lung Disease (CLD)

The use of postnatal steroids in very preterm infants is not uncommon. A survey of neonatologists in the United States revealed that 95% of them used steroids in preterm infants at risk for CLD.⁴⁸ A study reported that postnatal steroid use was 39% (range, 16% to 61%) in infants below 1000 g and 57% (range, 39% to 71%) in infants between 501 and 750 g.^{49,50} In KKH, out of the 83 extremely-low-birth-weight (ELBW) infants admitted to the NICU during 2001, 17 (21%) had received postnatal steroids; 33 (40%) had CLD at 28 days and 14 (17%) at 36 weeks' post conceptional age.

Inflammation appears to play a prominent role in the pathogenesis of CLD. Systemic corticosteroids have been widely used to treat CLD because of the anti-inflammatory effects of glucocorticoids. Steroids have a number of actions which could be beneficial in neonate with CLD. Systemic steroids have been shown to reduce pulmonary inflammatory mediators (polymorphs, macrophages, proteases, tumour necrosis factor and interleukins), inhibit the synthesis of prostaglandin and fibronectin. The other actions include enhanced surfactant synthesis, anti-oxidant production and β -adrenergic activity stabilisation of lysosomal and cellular membranes. These effects have been associated with reduction in pulmonary micro-vascular permeability, pulmonary oedema and mucous production.^{51,52}

Over the past two decades, a plethora of studies have evaluated the effects of postnatal steroids in infants with CLD. Initially, systemic steroid therapy was used in infants who were ventilator dependent beyond 3 to 4 weeks and in whom CLD was established.⁵³⁻⁵⁶ Subsequently, it was used at an earlier age (1 to 2 weeks of age) in attempts to minimise progression of CLD.⁵⁷⁻⁵⁹ Several studies⁶⁰⁻⁶² during the last decade have shown that pulmonary inflammation occurs early in the life of ELBW infants and this has led to very early use of systemic steroids during the first 3 to 4 days of life in the hope that earlier intervention would prevent the development of CLD.⁶³⁻⁶⁸ Thus, postnatal steroid therapy has been started as early as 2 hours of age and as late as 30 days of age in the various studies.

The reported clinical benefits from RCTs of postnatal steroid therapy were improvement in lung function and pulmonary mechanics, accelerated weaning from assisted ventilation, successful extubation and reduction in pulmonary interstitial emphysema, patent ductus arteriosus, supplemental oxygen exposure, CLD, intraventricular haemorrhage, mortality and length of hospital stay.^{69,70} In some infants, repeated courses of dexamethasone were required before successful extubation. However, a significant number of adverse events have been associated

with the use of systemic steroids in preterm infants. They include hyperglycaemia, hypertension, infection, ventricular hypertrophy, gastrointestinal bleeding and perforation, necrotising enterocolitis, nephrocalcinosis, ischaemic brain injury, osteopenia, increased protein catabolism, decreased growth and hypothalamic-pituitary-adrenal axis suppression.^{70,71} Dexamethasone was the commonest corticosteroid that was studied: in most of the studies an initial dose of 0.5 mg/kg/day or more was used and the duration of treatment varied between 3 and 42 days. In a multicentre randomised study⁶⁸ in ELBW infants, even a low initial dose of 0.15 mg/kg/day was associated with adverse effects, namely spontaneous gastrointestinal perforation (13% vs 4%), lower weight and smaller head circumference at 32 weeks. The high perforation rate appeared to be associated with concomitant indomethacin treatment. During the past 5 years, trials have reported adverse long-term neurodevelopmental sequelae including cerebral palsy in neonates who received steroid therapy very early in life.^{50,65,72-75} O'Shea et al¹⁵ have shown that infants treated with long course of dexamethasone (42 days) had significantly higher incidence of cerebral palsy (25%) compared to 7% in controls. The study by Shinwell et al⁷² has revealed that even shorter courses of dexamethasone (3 days) early in life was associated with significantly higher rate of cerebral palsy, (49% vs 15%). A study using 3-dimensional magnetic resonance imaging (MRI) technique has shown that the cerebral cortical gray matter volume in preterm infants treated with dexamethasone was reduced by 35% when compared against the controls.⁷⁶

Evidence from Cochrane Systematic Reviews

Halliday et al⁷⁷⁻⁷⁹ have reviewed 37 RCTs of postnatal corticosteroids for preventing or treating CLD in preterm infants and have classified them into three categories viz early postnatal (<96 hours), moderately early (7 to 14 days) and delayed (>3 weeks) groups. The main results of the above reviews are summarised in Table I. Thus, corticosteroids are beneficial in reducing CLD whether used prophylactically during the first 4 days of life or therapeutically later in infants with CLD. However, early steroid therapy has been associated with not only significant short-term adverse events (particularly gastro-intestinal perforation, hypertension), but also long-term neurodevelopmental sequelae such as cerebral palsy. Therefore, the practice of use of dexamethasone during the first few days of life to prevent CLD should be abandoned because the benefits do not outweigh the risks. The review has shown that the short-term adverse events of corticosteroids appear to be less frequent if they are used after 7 days of life and may not significantly increase the risk of adverse neurodevelopmental outcomes.⁷⁸ It should

TABLE I: POSTNATAL STEROIDS FOR PREVENTION OF CLD (COCHRANE REVIEW⁷⁷⁻⁷⁹)

Group	RCTs/Eligible infants	Significant benefits	Significant adverse effects (short-term)	Late outcomes
Early (<96 h)	21 trials/3072 infants ⁷⁷	• Earlier extubation • ↓ CLD at 28 days • ↓ CLD at 36 wks • ↓ PDA • Severe ROP • ↓ death or CLD at 28 days and 36 weeks	• ↑ gastrointestinal haemorrhage life • ↑ intestinal perforation • ↑ hyperglycaemia • ↑ hypertension	• ↑ cerebral palsy and abnormal neurological examination • Major neurosensory disability not significantly increased • Combined outcome of deaths or major neurosensory disability was not significantly increased
Moderately early (7 to 14 days)	7 trials/699 infants ⁷⁸	• ↓ mortality by 28 days • ↓ CLD at 28 days and 36 weeks • ↓ death or CLD at 28 days or 36 weeks • Earlier extubation	• ↑ hypertension • ↑ hyperglycaemia • ↑ gastrointestinal bleeding • ↑ infection • ↑ hypertrophic cardiomyopathy	• No significant increase in adverse neurological outcome
Delayed (>3 weeks)	9 trials/562 infants ⁷⁹	• ↓ in failure to extubate by 7 or 28 days • ↓ CLD at 36 weeks • ↓ death or CLD at 36 weeks • ↓ need for late rescue therapy with steroids • ↓ discharge to home oxygen	• ↑ glycosuria • ↑ hypertension • ↑ ROP (borderline significance)	• No increase in major neurosensory disability or combined rate of death or major neurosensory disability

CLD: chronic lung disease; PDA: patent ductus arteriosus; RCT: randomised controlled trials; ROP: retinopathy of prematurity; ↓: decreased; ↑: increased

be emphasised that most of the studies included in the reviews were designed to study short-term outcomes and only a few trials have reported follow-up and long-term outcome or post-discharge mortality of the infants studied. More prospective studies with long-term neuro-developmental follow-up are needed to prove or disprove that the benefits of systemic steroids outweigh the risks, particularly the long-term developmental sequelae. One such study, DART (Dexamethasone - A Randomised Trial), coordinated from Melbourne (Lex Doyle, Royal Women's Hospital), may throw more light on this issue when completed.

Corticosteroids for Post-extubation Laryngeal Oedema

Newborn infants requiring endotracheal intubation are susceptible to various types of laryngeal, subglottic and tracheal injuries including oedema, haemorrhage, inflammation, granuloma formation and ulceration of the mucosa. The laryngeal lesions occur predominantly in the posterior aspects of the glottic and subglottic region. All of the above lesions may contribute to the occurrence of post-extubation stridor and respiratory distress which may respond to nebulised racemic epinephrine or continuous positive airway pressure (CPAP) given using nasal-prongs. But if these measures fail, the infant may need reintubation. Dexamethasone, in view of its potent anti-inflammatory effects, may have a role in preventing or treating post-

extubation laryngeal oedema and reducing the need for subsequent reintubation and prolongation of stay in the NICU.

Preterm infants, who had multiple or traumatic endotracheal intubations or prolonged intubations of more than 14 days, are at high risk for airway oedema upon extubation. In such infants, Couser et al⁸⁰ have shown that prophylactic use of dexamethasone was associated with significantly less post-extubation stridor, reintubation and improved pulmonary function compared to controls. No significant side effect other than mild hyperglycaemia was noted in this trial. Multiple doses of dexamethasone (0.25 mg/kg 4 hours prior to extubation, then every 8 hours x 2 doses following extubation) may be more effective than a single dose given 30 minutes prior to extubation. Cochrane systematic reviews^{81,82} have been done to evaluate the role of corticosteroids for the prevention and treatment of post-extubation stridor in neonates. The reviewers have opined that there is no convincing benefit of prophylactic dexamethasone in VLBW infants who had shorter duration of intubation and who were at low risk for post-extubation laryngeal edema. On the other hand, in infants with prolonged intubation for more than 2 weeks or who had either traumatic or multiple intubations, a trend towards reduction in post-extubation stridor and successful extubations were demonstrated.^{81,82} In view of the potential long-term side effects of dexamethasone it would be prudent to restrict its use to infants who are at high risk for airway oedema.⁸²

Inhaled Steroid Therapy for Prevention of CLD

An alternative strategy to lessen the side effects of systemic corticosteroids is inhalation therapy. The more effective method of delivering corticosteroids topically is to use a metered-dose inhaler via an aerochamber connected to the endotracheal tube. Nebulisation of steroids is less efficacious in neonates compared to aerosol delivery using a metered-dose inhaler. Inhaled steroids have been used to prevent or treat CLD.

Beclomethasone, budesonide and fluticasone propionate have broad spectrum local anti-inflammatory effects and they have been studied in ventilated preterm infants. A study by Cole et al⁸³ suggested that inhaled beclomethasone was associated with 50% reduction in the need for subsequent systemic dexamethasone therapy, 40% reduction in bronchodilator therapy and 26% reduction in the need for mechanical ventilation at 28 days as well as reduction in inflammatory markers in tracheal aspirate. However, there was no reduction in the occurrence of CLD at 28 days or 36 weeks. Fok et al⁸⁴ have shown that in ventilated preterm infants, early inhaled fluticasone propionate facilitated extubation by day 14 compared to placebo infants (63% vs 31%). However, the incidence of CLD at 28 days or 36 weeks, and the need for subsequent systemic glucocorticoids or mortality was not significantly different between the groups. Yong et al⁸⁵ found that there was no evidence of any significant effect, either beneficial or detrimental, following 14 days of inhaled fluticasone propionate. To date, the largest steroid trial is the Open Study of Early Corticosteroids Treatment (OSECT)⁶⁷ where 570 preterm infants <30 weeks from 47 centres (including the above centre) were randomised to 4 treatment groups: early (<72 hours) dexamethasone or budesonide, selective late (>15 days) dexamethasone or budesonide. However, the study revealed that the primary outcome – death or CLD – at 36 weeks was not significantly different among the groups.

Systematic review⁸⁶ of inhaled versus systemic corticosteroids for preventing CLD in ventilated VLBW preterm infants revealed no statistically significant difference in the incidence of CLD and/or deaths at 28 days or 36 weeks. There was higher incidence of patent ductus arteriosus and the duration of mechanical ventilation and supplemental oxygen were significantly longer in the inhaled as compared to the systemic steroid group. Short-term adverse events, such as hyperglycaemia and gastrointestinal complications (haemorrhage, perforation), were lower in infants receiving inhaled steroids. Basal cortisol levels were decreased following beclomethasone therapy, but there was no evidence of adrenal suppression as evidenced by ACTH stimulation.⁸⁷ On the other hand, hypothalamic-

pituitary-adrenal axis suppression occurred following the use of fluticasone therapy.⁸⁸ The OSECT trial⁶⁷ reported poor weight gain in the early dexamethasone group as compared to the early inhaled budesonide therapy.

Inhaled Steroids in Neonates with Established CLD

Several authors⁸⁹⁻⁹¹ have studied the use of inhaled steroids in infants with CLD. The reported benefits included lowered respiratory rate, higher rate of successful extubation, improved dynamic compliance and reduction in airway resistance and these benefits occurred in infants ventilated at trial entry. However, significant reduction in duration of supplemental oxygen requirement was reported only in infants with severe bronchopulmonary dysplasia who were not ventilated at trial entry.⁹⁰ Systematic review of the 7 RCTs by Lister et al⁹² showed significant reduction in inability to extubate in infants treated with inhaled steroids administered for 1 to 4 weeks (OR, 0.12; 95% CI, 0.03 to 0.43) as compared to placebo. The risk of sepsis appeared similar between the 2 groups. Based on the above review, no firm conclusion could be derived with regard to the efficacy of inhaled steroids in non-ventilated infants. More studies with larger sample sizes are needed to assess the role of inhaled steroids in infants with CLD who require nasal-prong CPAP with or without oxygen. Whether this mode of therapy will reduce subsequent occurrence or severity of bronchial asthma also needs to be studied.

Alternative Steroid Treatment Strategies

Most clinical trials have used high-dose dexamethasone that were weaned over prolonged periods.⁹³ Hydrocortisone and methylprednisolone have been used in preterm infants at risk for CLD but without increase in adverse effects. Watterberg et al⁶⁶ have shown evidence of early adrenal insufficiency and increased lung inflammation in preterm infants who subsequently develop CLD. A randomised placebo controlled trial with low-dose hydrocortisone (1 mg/kg/day) treatment during the first 2 weeks of life increased survival without CLD and improved other measures of respiratory outcome, without apparent increase in adverse effects. The other alternative is the use of methylprednisolone which is a glucocorticoid with a shorter half-life and lower anti-inflammatory activity than dexamethasone and has no sulphiting agents.⁷⁵ In a study of 90 infants less than 30 weeks' gestation at risk for CLD, methylprednisolone was shown to be as effective as dexamethasone in weaning from mechanical ventilation but with fewer side effects including periventricular leukomalacia.⁹⁴ Large multicenter trials with long-term neurodevelopmental follow-up are needed to evaluate the benefits and safety of the above alternative therapeutic regimens.

Corticosteroids for Hypotension

Hypotension is a common occurrence in VLBW infants and is associated with intraventricular haemorrhage, periventricular leukomalacia and poor neurodevelopmental outcome.⁹⁵⁻⁹⁷ Hypotension is generally managed with volume expansion with normal saline or colloid, blood transfusion and inotropic support with dopamine or dobutamine. The aetiology of the hypotension in infants who do not have hypovolaemia as the cause is poorly understood. Evidence suggests a pivotal role for corticosteroids in mediating the effects of endogenous catecholamines. Some preterm infants have immature corticosteroid stress response. A randomised trial, comparing the efficacy of dopamine and low-dose hydrocortisone in hypotensive VLBW infants, has shown that the efficacy of the drugs was comparable (81% vs 100%); the incidences of hyperglycaemia, sepsis, necrotising enterolitis (NEC) and adrenal suppression did not differ between the groups.⁹⁸ A retrospective study has also shown that preterm infants with pressor-resistant hypotension respond to hydrocortisone with rapid normalisation of the cardiovascular status and sustained decreases in volume and inotropic requirement.⁹⁹ Proposed mechanism of action by which corticosteroids improve blood pressure includes enhancement of vascular sensitivity to catecholamines, increase in β -adrenergic receptor numbers, induction of key enzymes in catecholamine synthesis and enhanced adenyl cyclase activity following agonist stimulation and enhanced gene transcription.⁹⁹⁻¹⁰¹

Adrenocortical insufficiency leading to severe hypotension and circulatory collapse has been demonstrated in extremely preterm infants.¹⁰¹ The hypotension is refractory to volume expansion and inotrope treatment but respond promptly to low-dose hydrocortisone (1 mg/kg/dose given every 4 hours). In contrast to the classical Addisonian crisis, adrenocortical insufficiency in preterm infants is likely to be transient and requires only short duration (5 to 7 days) of replacement therapy. Other investigators also have reported similar effects with physiological doses of hydrocortisone or even with one dose of dexamethasone.¹⁰²⁻¹⁰⁴

Conclusion

The place for single course of corticosteroids administered 24 hours to 1 week prior to premature delivery is now well established. The practice of repetitive dosing is controversial, in view of evidence of adverse effects coming not only from animal models but also from some human data. It is currently recommended that the obstetrician limit the prescribing of antenatal steroids to a single course for women at risk of preterm delivery between 23 and 34 weeks of gestation (or 36 weeks as in the UK¹⁰⁵ and

Singapore guidelines). There is a need to evaluate the use of multiple courses of ACS in clinical trials.

Postnatal systemic corticosteroids in physiological doses may have a place in very preterm infants with refractory hypotension and in pharmacological doses to those infants who are high risk for airway oedema. Even though systemic corticosteroids have shown benefits in reducing CLD and improving survival, there are increasing concerns about the long-term neurologic problems, particularly cerebral palsy in survivors. More research with long-term neurodevelopmental follow-up is urgently needed to resolve this issue. Inhaled steroids may prove to be a safer option but more studies are required to find out the right inhalation device, optimal dose and duration of treatment. Until then, routine use of systemic steroids for the prevention or treatment of CLD in preterm infants is not recommended. A short course of low-dose dexamethasone may be considered with caution on a case-by-case basis, for infants who are oxygen- and ventilator-dependent for more than 2 weeks. In each case, the neonatologist must balance the benefits of earlier extubation, reduced risks of CLD and improved survival against the potential risk of adverse neurodevelopmental outcome. It may be prudent for 2 consultant neonatologists to agree before prescribing pharmacologic dose of corticosteroids to preterm infants.

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