**Early Prophylactic Postnatal Hydrocortisone**

Bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) is a major morbidity of very preterm birth, associated with increased risk for a range of adverse outcomes, including respiratory complications, growth failure, neurodevelopmental impairment (NDI), and death. In contrast to many other morbidities of preterm infants, the incidence has not decreased over time and in reality may be increasing.

Evidence of early lung inflammation in infants developing BPD had led to early treatment with high doses of anti-inflammatory corticosteroids such as dexamethasone, resulting in short-term improvement and improved survival but unacceptable short-term and long-term adverse effects, such as cerebral palsy (CP). The use of lower doses and alternative corticosteroid formulations to dexamethasone may improve the risk to benefit ratio.

The Cochrane Meta-analysis looking at early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infantsfound thatdexamethasone treatment in the first 8 days almost doubled the risk of cerebral palsy (CP), RR 1.75 [ 1.20, 2.55 ] (921 infants studied). In contrast, with hydrocortisone treatment in the first 8 days no difference was found in CP risk compared with placebo RR 1.05 [ 0.66, 1.66 ] (1052 infants studied). In addition, hydrocortisone reduced mortality to discharge (typical RR hydrocortisone 0.80, 95% CI 0.65 to 0.98; 11 studies, 1433 infants), whereas no significant improvement in survival was found with dexamethasone 1

According to Vermont Oxford Network (VON) analysis the median rates for chronic lung disease (CLD) in the SW ODN in 2017 was, by gestation: 23 weeks (100%), 24 weeks (100%), 25 Weeks (100%) 26 weeks (71%), 27 weeks (83%) and 28 weeks (31%). 79% of infants below 30 weeks gestation received mechanical ventilation, 5% received inhaled nitric oxide and 18% were discharged home on oxygen. In the 24-26 week gestation cohort (n=94) 10% received dexamethasone for CLD (in the highest quarter of units 33% of 24-26 week gestation infants received dexamethasone).

In summary: Chronic Lung Disease is a common complication of prematurity in our South-West ODN, with significant long-term impact (1 in 5 babies were discharged home on oxygen). Dexamethasone is widely used for CLD.

Data reported since 1995 have supported the hypothesis that very preterm infants who develop BPD/CLD often have relative adrenal insufficiency during the first postnatal week, suggesting that early hydrocortisone replacement could be beneficial. 2,3 Among 11 randomized controlled trials (RCTs) that included hydrocortisone treatment initiated before 7 postnatal days in very preterm infants, 5 were designed specifically to test the efficacy of early prophylaxis of early adrenal insufficiency to improve survival without BPD/CLD. 4,5,6,7,8 These trials extended hydrocortisone therapy beyond the first postnatal week and used a dose of 1-2 mg/kg/day, which has been shown to moderately but significantly increase serum cortisol concentrations in extremely preterm neonates compared with placebo. 4

In a large individual patient data meta-analysis of 4 RCTs (n = 982), early low-dose hydrocortisone treatment for 10-15 days was associated with a significant increase in survival without BPD (OR, 1.45; 95% CI, 1.11-1.90), and a 30% reduction in death (all causes) before discharge (OR, 0.70; 95% CI, 0.51-0.97). 9 The hydrocortisone therapy was associated with an increased risk of spontaneous gastrointestinal perforation (OR, 2.50; 95% CI, 1.33-4.69) when given in association with indomethacin exposure. The incidence of late-onset sepsis was increased in infants exposed to hydrocortisone (OR, 1.34; 95% CI, 1.02-1.75), but despite this no adverse effects were reported for either death or 2-year neurodevelopmental outcomes as assessed in an aggregate meta-analysis. The majority of patients in the intervention arms in these RCTs received hydrocortisone 1mg/kg/day (for 7-12 days) followed by 0.5mg/kg/day for 3 days.

PREMILOC, the largest of the RCTs in the IPD meta-analysis, found that the incidence of cerebral palsy or other major neurological impairments was not significantly different between hydrocortisone and placebo groups overall. 10 Among surviving infants born at 24–25 weeks, a significant improvement in global neurological assessment was observed in the hydrocortisone group compared with the placebo group (p=0.02) with a risk of moderate-to-severe NDI of 2% and 18%, respectively (risk difference 16 (95% CI −28% to −5%)). 11

Conclusion: Prophylactic hydrocortisone reduces CLD/BPD and improves survival without increasing the risk of cerebral palsy or neurodevelopmental impairment. In the highest risk, lowest gestation infants there are potential improvements in neurodevelopmental outcomes with use of early low-dose hydrocortisone. The use of early low-dose hydrocortisone is likely to reduce the relatively high CLD rates in the SW ODN and might reduce the exposure to postnatal dexamethasone rescue treatment for severe BPD, with its known neurotoxic side effects.

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