Re-evaluating postnatal steroids for very preterm infants to prevent lung disease

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[1228 words]

Compared with the universal acceptance of antenatal steroids as an inexpensive, safe and highly effective way of enhancing neonatal survival and reducing morbidity in preterm infants, the use of steroids after birth has been more controversial,[1] and there remains uncertainty about which steroid to use, indications, safety and dosage.

Neonatal bronchopulmonary dysplasia (BPD) or chronic lung disease is the most common neonatal complication following extremely preterm (<28 weeks gestational age) or extremely low birthweight (<1000 g) birth and around half of these infants are receiving supplemental oxygen at 36 weeks post menstrual age. Chronic respiratory morbidity remains with the child throughout life. Children with more severe neonatal lung disease have poorer respiratory function in early adolescence[2] and likely also to have respiratory morbidity in adult life[3]. The consequences of BPD are not confined to the respiratory system but associated with other neonatal morbidities, such as persistence of the ductus arteriosus and increased risk of neonatal sepsis. Children with neonatal BPD have higher rates of neurologic morbidity at follow up, poor postnatal growth, and evidence of increased cardiovascular risk. Preventing BPD is thus a priority in neonatal medicine and is likely to have benefit beyond only respiratory outcomes.

Despite the high prevalence of BPD among the increasingly immature population of infants surviving preterm birth, no drugs have been licensed to prevent this condition. Vitamin A was studied specifically as a preventive agent and showed a significant reduction in the frequency of BPD[4]. However, the injections are painful and limited long-term outcome data are available;

because of this vitamin A has not found widespread acceptance by the neonatal community. A trial evaluating the safety of neonatal caffeine treatment demonstrated reduction in rates of BPD,[5] together with reassuring safety data at 2 and 5 years of age[6], and is now used in clinical practice. Set against these examples, knowledge of the early and late effects of neonatal steroid administration to prevent or treat BPD remains unclear.

The use of dexamethasone in the second or third week after birth, initially successful in weaning infants from mechanical ventilation, was subject to enthusiastic overuse in the late 1990s. Following development of concern about adverse long-term neurodevelopmental outcomes,[7] there was a rapid decline in use of dexamethasone and an increase in the prevalence of BPD. Over time, more information about this intervention became available, and a 2014 systematic review suggested that using corticosteroids after 7 days of age may reduce neonatal mortality without increasing the risk of long-term neurologic disability, although the power of any of the included studies to demonstrate safety was limited[8]. Attempts to study lower doses of dexamethasone, seemingly as effective as the higher doses investigated, have failed to date due to under-recruitment,[9] even though many clinicians now use such a regimen. Other clinicians have used hydrocortisone in short courses, rather than dexamethasone, and anecdotally claim it to be as effective, but this use is not based on robust trial evidence[10].

Along with this rescue approach for infants with established severe respiratory disease, other investigators have studied the early use of steroids in 2 situations – to prevent BPD and to reverse hypotension. These are very different aims. However, given the anxiety about the

potential long-term effects from the use of postnatal steroids, it would seem incumbent on all trials to provide high-quality follow-up data and to power such studies to demonstrate that the use of steroids, for either indication, is safe. In one early trial, nearly half of the survivors after a 3-day course of dexamethasone appear to have developed cerebral palsy, compared with 18% in the control group[11]. However, most of the studies have been too small to determine safety, even if they provided long-term outcome data. Determining long-term safety is often forgotten in the design of neonatal trials, but it is of utmost importance. Few trials of early administration of neonatal steroids have reported outcomes beyond 2 years, yet there is evidence of potential long-term harm in the 2 largest trials carried out in the 1990s, both using dexamethasone either as a 3 or 28 day course[12].

In this issue of *JAMA*, Baud and colleagues report important and reassuring data from a trial of early neonatal low-dose hydrocortisone to prevent chronic lung disease or BPD, detailing secondary safety outcomes at 2 years of age[13]. The Early Low-Dose Hydrocortisone to Improve Survival without Bronchopulmonary Dysplasia in Extremely Preterm Infants (PREMILOC) trial is important as it is, to date, the largest investigation of hydrocortisone to prevent BPD and previously reported a 9 percentage point increase in survival without BPD at 36 weeks (primary outcome)[14], a similar effect size to vitamin A and caffeine. This outcome was achieved using the lowest dose of hydrocortisone yet investigated. In the current report, a high rate of follow up was achieved (379 of 406 survivors; 93%) at a median 22 months corrected age. The rates of potential neonatal complications of steroids were not increased in the group exposed to hydrocortisone. Although the trial was not powered for secondary outcomes, there was no

significant difference in the frequency of pre-specified neurodevelopmental impairment (NDI) between the infants who received hydrocortisone and those who received placebo (hydrocortisone group: no NDI, 73%; mild NDI, 20%; moderate-to-severe NDI, 7%; placebo group: no NDI, 70%, mild NDI, 18%; moderate-to-severe NDI, 11%; P=0.37). The posthoc outcome of mean global developmental index was also not significantly different between groups (91.7 in hydrocortisone group vs 91.4 in placebo group), and the 95% confidence interval for the difference (0.3, 95% CI, -2.7 to 3.4) reassuringly was within the 5-point minimal clinically important difference. Growth and respiratory outcomes were similarly distributed between the 2 groups.

Thus, early use of low-dose hydrocortisone holds promise as an intervention to prevent BPD. However, the systematic review[12] found steroid-related short-term complications, including gastrointestinal bleeding and perforation, although those complications were not seen in the current trial. A re-evaluation of early neonatal therapy is warranted. Other groups are encouraged to confirm the findings of the PREMILOC trial, using a very low dose of hydrocortisone and powering their studies to investigate safety outcomes. The PREMILOC investigators are planning later outcome studies at 5-7 years of age. Until those and other trials are completed, the value of early hydrocortisone to safely prevent BPD appears promising but remains unclear.

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