

Rescue Glucocorticoid Therapy in Extremely Preterm Infants

Review Article

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Abstract

Refractory hypotension and chronic lung disease are common and lethal complications in extremely low gestational age newborns. Recently, glucocorticoids have been used as rescue therapy for these diseases based on the proposed contribution of relative adrenal insufficiency. However, the efficacy and safety, and optimal treatment protocol of glucocorticoids have not been established. We recently reported the potency of our therapeutic protocol for postnatal refractory hypotension with a single low dose of hydrocortisone. We also reported the efficacy of our therapeutic protocol with hydrocortisone for severe leaky lung syndrome, which occurs in the progression phase of chronic lung disease. To determine the efficacy and safety of these strategies, further well-designed randomized controlled trials are necessary.

Keywords: Glucocorticoid; Extremely Preterm Infants; Refractory Hypotension; Chronic Lung Disease.

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Introduction

Despite the recent improvement in survival in extremely low gestational age newborns (ELGAN), postnatal refractory hypotension and chronic lung disease (CLD) are still common complications of ELGAN, and are associated with devastating neurodevelopmental outcomes [1]. Although the pathophysiology of these morbidities has not been fully clarified, the potential contribution of relative adrenal insufficiency in preterm newborns to the development of refractory hypotension and CLD has been suggested [2]. Based on this possibility, a series of glucocorticoid (GC) therapies for ELGAN have been investigated, but the efficacy and safety of GC for morbidity are still unclear [3-5]. In this mini review, we focus on the rescue use (not prophylactic use) of GC for postnatal refractory hypotension and CLD in ELGAN, and review our clinical practices.

Rescue GC Therapy for Refractory Hypotension

Refractory hypotension commonly occurs in premature newborns. Refractory hypotension is associated with a high mortality rate, an increased incidence of intraventricular hemorrhage and periventricular leukomalacia, and poor neurodevelopmental outcomes. However, the etiology of refractory hypotension is not fully understood [6-10]. Our research group and others have recently focused on "relative adrenal insufficiency", as the basis of refractory hypotension in ELGAN [11]. This research is based on findings of an inverse relationship between plasma cortisol levels and gestational age [12], and an insufficient response to stress in sick, ventilated, very preterm infants [13]. There are several retrospective trials regarding rescue GC therapy to treat neonatal refractory hypotension [14-16]. However, there are insufficient numbers of well-designed randomized controlled trials (RCTs) regarding GC therapy for refractory hypotension in preterm infants [3]. Among the four RCTs included in a recent Cochrane Review [3], Gaissmaier et al. used dexamethasone (DEX) [17] and Ng et al. used hydrocortisone (HC) [18] are intended to treat early neonatal refractory hypotension by GC therapy. The authors in both of the trials concluded that GC therapy significantly reduced the use of inotropes in the management of refractory hypotension. However, their study designs were not sufficient to determine the safety of rescue use of GC. With regard to studies using HC as the primary treatment of hypotension (not for hypotension unresponsive to inotropes), Bourchier et al. compared HC versus dopamine in a randomized controlled manner with a relatively small sample size, and found no significant advantage of HC against dopamine use [19]. Hochwald et al. investigated the combinational therapy of HC with dopamine against placebo with dopamine in a RCT, and found no significant differences in efficacy and safety between the groups [20].

Therefore, there is insufficient evidence on the safety and efficacy of rescue GC therapy for refractory hypotension in preterm infants [3]. We have reserved GC therapy as second-line treatment for patients with intractable hypotension who are not responsive to volume expansion and inotropes at Kobe Children's Hospital Perinatal Center. Because of the concern about the adverse effects of DEX on long-term neurological outcome, we adopted HC as first-line treatment of GC therapy for ELGAN [4,21,22]. We defined refractory hypotension as a mean arterial pressure less than 30 mmHg for newborns with a gestational age between 25 and 27 weeks, and less than 25 mmHg for newborns with a gestational age between 23 and 24 weeks, even after appropriate inotropic management with a volume expander (>10mL/kg) and inotrope (dopamine >5µg/kg/min) [23]. We administered HC at a dose of 2mg/kg for cases of refractory hypotension, and repeated doses were administered at least 12 hours apart if hypotension persisted. According to this protocol, we could achieve a mean arterial pressure in patients with refractory hypotension that was increased to levels that were comparable with those of patients without hypotension at 5 hours after HC treatment (>30mmHg). Additionally, normal arterial pressure levels were maintained through 12 h after the treatment, without an increased incidence of complications, including intestinal perforations, intraventricular hemorrhage, or hyperglycemia [23]. Our protocol used a lower total dose of GC administrations compared with previous studies [18-20]. We also showed a sufficient inotropic effect in ELGAN without a significant increase in devastating complications. Therefore, we believe that this protocol is potent and has some advantages with respect to safety of GC therapy.

Rescue GC Therapy for CLD

The incidence of CLD is approximately 40% in extremely low birth weight infants [1], and is associated with mortality and poor neurodevelopmental outcomes [24-25]. The pathogenesis of CLD is regarded as multifactorial, including infection/inflammation, oxidative stress, barotrauma/volutrauma, genetic factors, and the absence of antenatal steroids [26,27]. Antenatal exposure of GC improves subsequent pulmonary function after preterm delivery. However, the effect of antenatal GC is not proportionally augmented by multiple doses [28,29]. Intriguingly, antenatal GC treatment can modulate the amplitude of pulsatile cortisol secretion in premature infants [30]. Recently, Wetterberg et al. proposed that early adrenal insufficiency was the basis of CLD, based on their finding that infants who subsequently developed CLD had significantly lower cortisol secretion in response to adrenocorticotropic hormone than those without CLD [31]. Based on these findings, GC therapy has been undertaken for prophylactic or therapeutic purposes for CLD, but its efficacy and safety have still not been fully clarified. In the Cochrane Review including 21 RCTs regarding late (>7 days) postnatal corticosteroids for CLD in preterm infants, Dyle et al. concluded that late GC therapy may reduce neonatal mortality without significantly increasing the risk of adverse long-term neurodevelopmental outcomes [5]. However, the quality of studies determining the long-term outcome is limited. Dyle et al. also performed a systematic review including 29 RCTs on early (<8 days) postnatal corticosteroids for preventing CLD in preterm infants [4]. They concluded that use of early corticosteroids, especially DEX, for treatment or prevention, should be curtailed until more research has been performed. Therefore, only therapeutic GC use is currently warranted. However, evidence on the rescue use of GC for the "progression"

phase of CLD is still limited.

In the 1990s, Swischuk et al. proposed the entity named leaky lung syndrome (LLS). This syndrome is characterized by pulmonary edema in ventilated infants due to increased permeability of capillaries in the lungs, resulting in fluids leaking into the pulmonary interstitium [32,33]. They differentiated LLS from bubbly dysplastic lungs of CLD. Although they proposed that LLS is a distinct clinical entity, pulmonary edema is common in infants in the progression phase of CLD. Therefore, recently, we defined the progression phase of comorbid CLD with massive pulmonary edema as "severe LLS", and reported a high incidence (>40%) of severe LLS in ELGAN [34]. Because glucocorticoids play a role in maintaining vascular tone and its permeability [35-37], we performed a pilot study to determine the efficacy of HC therapy for severe LLS. In this pilot study, we adopted a HC therapy regimen with an initial dose of 4mg/kg/day and tapered it for 2-3 weeks. This protocol was modified from the regimen described by van der Heide-Jalving [38] and has been used as a rescue therapy for acute deterioration of CLD in our center. We showed that HC therapy effectively reduced the amount of tracheal secretion and oxygen dependency in ELGAN with severe LLS [34]. Although this was preliminary study with a small number of samples, these results suggested that HC therapy is effective for treating CLD in the progression phase by improving pulmonary permeability.

Summary

We reviewed rescue GC therapy for refractory hypotension and CLD in ELGAN and described our therapeutic strategy of using HC. We consider that our single low-dose HC treatment is effective and safe for treating refractory hypotension. Additionally, our rescue HC therapy regimen is effective in treating not only acute deterioration of CLD, but also the progression phase of CLD. To clarify the pathophysiology of these entities and to determine the effect of HC therapy on them and the long-term safety of HC, further well-designed RCTs are necessary.

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