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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 adrenocorticotrophic 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.

References

[1]. Eichenwald EC, Stark AR (2008) Management and outcomes of very low birth weight. N Engl J Med 358: 1700-1711.

[2]. Fernandez EF, Watterberg KL (2009) Relative adrenal insufficiency in the preterm and term infant. J Perinatol 29 Suppl 2: S44-49.

[3]. Ibrahim H, Sinha IP, Subhedar NV (2011) Corticosteroids for treating hypotension in preterm infants. Cochrane Database Syst Rev: CD003662.

[4]. Doyle LW, Ehrenkranz RA, Halliday HL (2014) Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev 5: CD001146.

[5]. Doyle LW, Ehrenkranz RA, Halliday HL (2014) Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev 5: CD001145.

[6]. Watkins AM, West CR, Cooke RW (1989) Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. Early Hum Dev 19: 103-110.

[7]. Goldstein RF, Thompson RJ, Jr., Oehler JM, Brazy JE (1995) Influence of acidosis, hypoxemia, and hypotension on neurodevelopmental outcome in very low birth weight infants. Pediatrics 95: 238-243.

[8]. Fanaroff JM, Fanaroff AA (2006) Blood pressure disorders in the neonate: hypotension and hypertension. Semin Fetal Neonatal Med 11: 174-181.

[9]. Laughon M, Bose C, Allred E, O'Shea TM, Van Marter LJ, et al. (2007) Factors associated with treatment for hypotension in extremely low gestational age newborns during the first postnatal week. Pediatrics 119: 273-280.

[10]. Subhedar NV (2003) Treatment of hypotension in newborns. SeminNeonatol 8: 413-423.

[11]. Watterberg KL (2004) Adrenocortical function and dysfunction in the fetus

and neonate. SeminNeonatol 9: 13-21.

[12]. Scott SM, Watterberg KL (1995) Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants. Pediatr Res 37: 112-116.

[13]. Huysman MW, Hokken-Koelega AC, De Ridder MA, Sauer PJ (2000) Adrenal function in sick very preterm infants. Pediatr Res 48: 629-633.

[14]. Baker CF, Barks JD, Engmann C, Vazquez DM, Neal CR, Jr., et al. (2008) Hydrocortisone administration for the treatment of refractory hypotension incritically ill newborns. J Perinatol 28: 412-419.

[15]. Seri I, Tan R, Evans J (2001) Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. Pediatrics 107: 1070-1074.

[16]. Rutkowska M, Resko-Zachara M, Adamska E, Oltarzewski M, Szamotulska K (2008) [Cortisol concentration, hypotension and treatment of cardiovascular insufficiency in the first days of life of very preterm newborns - preliminary report]. Med Wieku Rozwoj 12: 950-957.

[17]. Gaissmaier RE, Pohlandt F (1999) Single-dose dexamethasone treatment of hypotension in preterm infants. J Pediatr 134: 701-705.

[18]. Ng PC, Lee CH, Bnur FL, Chan IH, Lee AW, et al. (2006) A double-blind, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. Pediatrics 117: 367-375.

[19]. Bourchier D, Weston PJ (1997) Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 76: F174-178.

[20]. Hochwald O, Palegra G, Osiovich H (2014) Adding hydrocortisone as 1st line of inotropic treatment for hypotension in very low birth weight infants. Indian J Pediatr 81: 808-810.

[21]. Yeh TF, Lin YJ, Hsieh WS, Lin HC, Lin CH, et al. (1997) Early postnatal dexamethasone therapy for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome: a multicenter clinical trial. Pediatrics 100: E3.

[22]. Shinwell ES, Karplus M, Zmora E, Reich D, Rothschild A, et al. (1996) Failure of early postnatal dexamethasone to prevent chronic lung disease in infants with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 74: F33-37.

[23]. Mizobuchi M, Yoshimoto S, Nakao H (2011) Time-course effect of a single dose of hydrocortisone for refractory hypotension in preterm infants. Pediatr Int 53: 881-886.

[24]. Singer L, Yamashita T, Lilien L, Collin M, Baley J (1997) A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. Pediatrics 100: 987-993.

[25]. Stevenson DK, Wright LL, Lemons JA, Oh W, Korones SB, et al. (1998) Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. Am J Obstet Gynecol 179: 1632-1639.

[26]. Kinsella JP, Greenough A, Abman SH (2006) Bronchopulmonary dysplasia. Lancet 367: 1421-1431.

[27]. Fujioka K, Shibata A, Yokota T, Koda T, Nagasaka M, et al. (2014) Association of a vascular endothelial growth factor polymorphism with the development of bronchopulmonary dysplasia in Japanese premature newborns. Sci Rep 4: 4459.

[28]. Jobe AH, Newnham JP, Willet KE, Sly P, Ervin MG, et al. (2000) Effects of antenatal endotoxin and glucocorticoids on the lungs of preterm lambs. Am J Obstet Gynecol 182: 401-408.

[29]. Polk DH, Ikegami M, Jobe AH, Sly P, Kohan R, et al. (1997) Preterm lung function after retreatment with antenatal betamethasone in preterm lambs. Am J Obstet Gynecol 176: 308-315.

[30]. Arnold JD, Bonacruz G, Leslie GI, Veldhuis JD, Milmlow D, et al. (1998) Antenatal glucocorticoids modulate the amplitude of pulsatile cortisol secretion in premature neonates. Pediatr Res 44: 876-881.

[31]. Watterberg KL, Scott SM (1995) Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. Pediatrics 95: 120-125.

[32]. Swischuk LE, John SD (1996) Immature lung problems: can our nomenclature be more specific? AJR Am J Roentgenol 166: 917-918.

[33]. Swischuk LE, Shetty BP, John SD (1996) The lungs in immature infants: how important is surfactant therapy in preventing chronic lung problems? Pediatr Radiol 26: 508-511.

[34]. Mizobuchi M, Iwatani S, Sakai H, Yoshimoto S, Nakao H (2012) Effect of hydrocortisone therapy on severe leaky lung syndrome in ventilated preterm infants. Pediatr Int 54: 639-645.

[35]. Watts CL, Bruce MC (1992) Effect of dexamethasone therapy on fibronectin and albumin levels in lung secretions of infants with bronchopulmonary dysplasia. J Pediatr 121: 597-607.

[36]. Thompson BT (2003) Glucocorticoids and acute lung injury. Crit Care Med 31: S253-257.

[37]. Ke YW, Gu MN, Liu QH, Xu JS, Wan SH (2011) Effect of methylprednisolone pretreatment on pulmonary permeability and dipalmitoylphosphatidylcholine content in rabbits with reexpansion pulmonary edema. Nan Fang Yi Ke Da Xue Xue Bao 31: 1090-1092.

[38]. van der Heide-Jalving M, Kamphuis PJ, van der Laan MJ, Bakker JM, Wiegant VM, et al. (2003) Short- and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? Acta Paediatr 92: 827-835.