

# Postnatal oral hydrocortisone in treatment of bronchopulmonary dysplasia: an observational study

Banu MÜTLÜ, Gonca SANDAL, Gözde KANMAZ, Zeynep ERASLAN, Ömer ERDEVE, Şerife Suna OĞUZ, Uğur DİLMEN

Ankara Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Yenidoğan Yoğun Bakım Ünitesi, Ankara.

## ÖZET

**Bronkopulmoner displazi tedavisinde postnatal oral hidrokortizon tedavisi: Gözlemsel bir çalışma**

**Giriş:** Çalışmamızın amacı, bronkopulmoner displazi tedavisi için hidrokortizonun düşük dozda bile etkili ve güvenli bir alternatif tedavi olduğunu belirlemektir.

**Materyal ve Metod:** Bu prospektif pilot çalışma Dr. Zekai Tahir Burak Kadın Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesindeki üçüncü düzey yenidoğan yoğun bakım ünitesinde yapıldı. Yaklaşık olarak üç hafta ve üstünde ventilatör bağımlılığı olan (kurtarma tedavisi olarak tanımlandı) veya postkonsepsiyonel 36. haftada herhangi bir infeksiyon kanıtı olmadan oksijen bağımlılığı devam eden (bronkopulmoner displazi tedavisi olarak tanımlandı) preterm bebekler (< 32 gebelik haftası veya < 1500 g doğum ağırlığı) çalışmaya alındı. Hidrokortizon, ilk hafta başlama dozu 1 mg/kg günde iki kez oral olarak, daha sonra klinik yanıtı göre %10-20 azaltılarak uygulandı.

**Bulgular:** Toplam 90 infant çalışmaya alındı. Hidrokortizon tedavisinden sonra sadece üç hasta solunumsal destek alıyordu. İlacın güvenilirliği değerlendirildiğinde 8 (%8.8) infantta hidrokortizon tedavisinin erken komplikasyonu gözlemlendi.

**Sonuç:** Çalışmamız, bildiğimiz kadarıyla literatürde bronkopulmoner displazi tedavisinde hidrokortizon dozu ve başlama zamanı açısından ilk çalışmadır.

**Anahtar Kelimeler:** Bronkopulmoner displazi, hidrokortizon, preterm infant.

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## Yazışma Adresi (Address for Correspondence):

Dr. Gonca SANDAL, Ankara Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Yenidoğan Yoğun Bakım Ünitesi, ANKARA - TÜRKİYE  
e-mail: kocabasgonca@mynet.com

## SUMMARY

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Banu MÜTLÜ, Gonca SANDAL, Gözde KANMAZ, Zeynep ERASLAN, Ömer ERDEVE,  
Şerife Suna OĞUZ, Uğur DİLMEN

Neonatal Intensive Care Unit, Ankara Dr. Zekai Tahir Burak Woman Health and Diseases Training and Research Hospital, Ankara, Turkey.

**Introduction:** The aim of our study was to determine whether hydrocortisone even at low dose could be an effective and safe alternative treatment for bronchopulmonary dysplasia.

**Materials and Methods:** This prospective pilot study was conducted in a tertiary referral neonatal intensive care unit placed in Ankara Zekai Tahir Burak Maternity Teaching Hospital. Preterm babies (< 32 week gestational age or < 1500 g birth weight) who were ventilator dependent approximately at or beyond three weeks of age (defined as rescue treatment) or were oxygen dependent on postmenstrual 36<sup>th</sup> week without evidence of any infection (defined as bronchopulmonary dysplasia treatment) were enrolled in the study. Hydrocortisone was used orally in an initial dose of 1 mg/kg twice a daily for a week and then the dose was tapered by 10-20% every other day regarding to clinical response.

**Results:** A total of 90 infants were enrolled in this study. After hydrocortisone treatment only 3 (3.4%) patients were still on respiratory support. When safety of the drug was evaluated 8 (8.8%) infants had early complications of hydrocortisone treatment.

**Conclusion:** To the best of our knowledge this study is the first trial in the literature along with the hydrocortisone dose and the initiation time in treatment of bronchopulmonary dysplasia.

**Key Words:** Bronchopulmonary dysplasia, hydrocortisone, preterm infant.

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## INTRODUCTION

Remarkable advances in the treatment of neonatal respiratory disorders, such as antenatal glucocorticoid therapy and alternative modes of ventilation, have reduced neonatal mortality and acute respiratory morbidity. However, bronchopulmonary dysplasia (BPD) remains as a substantial complication, especially among the most immature infants. Since inflammation plays a prominent role in pathogenesis of BPD, intravenous and oral steroids have been used as anti-inflammatory agents to alter the course of lung disease in premature infants (1-3).

Among all corticosteroids, dexamethasone has been well studied and has been found effective in weaning infants off mechanical ventilation when given moderately early (7-14 days of age) or late (14-28 days of age) in the initial nursery course (1-3). Despite this effect, dexamethasone therapy has not been shown to reduce the total days of hospitalization, duration of supplemental oxygen therapy or incidence of BPD (1). Unfortunately, dexamethasone therapy has been associated with an increase in cerebral palsy (CP) and other neurodevelopment impairments (NDI) at follow-up

(1,4,5). Recent articles have suggested hydrocortisone as a safer alternative to dexamethasone in treating and preventing BPD, partly on the basis of data from observational long-term studies of fewer adverse behavioral, cardiovascular, neurological and immune outcomes, among others, in childhood (6-10). There has been a requirement to determine whether and on which doses hydrocortisone therapy is effective in treating BPD, and whether it is free of the adverse effects associated with systemic dexamethasone therapy.

This study was designed on the hypothesis of whether hydrocortisone even at low dose could be an effective and safe alternative treatment for BPD.

## MATERIALS and METHODS

This prospective study was conducted in a tertiary referral neonatal intensive care unit (NICU) placed in Ankara Dr. Zekai Tahir Burak Maternity Teaching Hospital. The study was approved by the local Research Ethics Committee. Between January 2008 and August 2010 infants with BPD were recruited to this study. Infants were excluded if they had a diagnosis of suspected or proven infection, significant congenital malformation, and clinical evidence of PDA, NEC and intesti-

nal hemorrhage or perforation. Parental informed consent was obtained for all enrolled patients.

Patient characteristics (gestational week, birth weight, gender, type of delivery etc.), maternal, prenatal and postnatal features, complications including infection, hyperglycemia, glycosuria, hypertension, necrotizing enterocolitis (NEC), gastrointestinal perforation, intraventricular hemorrhage (IVH), severe retinopathy of prematurity (ROP) were all recorded.

Preterm babies (< 32 week gestational age or < 1500 g birth weight) who were ventilator dependent approximately at or beyond three weeks of age (defined as rescue treatment) or were oxygen dependent on postmenstrual 36<sup>th</sup> week without evidence of any infection (defined as BPD treatment) were enrolled in the study. Hydrocortisone was used orally in an initial dose of 1 mg/kg twice a daily for a week and then the dose was tapered by 10-20% every other day regarding to clinical response. Clinical response was defined as reduced supplemental oxygen requirement (< 30%) and/or weaning from respiratory support (ventilation/n CPAP).

The major outcomes of the study were the efficacy and safety of the hydrocortisone treatment for BPD on 1 mg/kg dose beyond the third week of life. Patients who reached 12 months were evaluated for neurodevelopment. Development was assessed with the Bayley Scales of Infant Development II. Mental Development Index (MDI) or Psychomotor Development Index (PDI) > 2 SD below the mean (ie, < 70) was defined as abnormal. All Bayley II examiners were previously certified.

## RESULTS

A total of 90 infants were enrolled in this study. Of these, 3 died during the hospitalization and left 87 were available for follow-up. Among these infants, 37 (42.5%) who reached 12 months adjusted age were evaluated for long-term neurodevelopmental outcome.

The demographic and clinical features of the patients are summarized in Table 1. Maternal demographic characteristics are summarized in Table 2. Thirty two

**Table 1. Maternal demographic features.**

Age (mean ± SD, years)	26.8 ± 5.06
Antenatal steroid treatment, n (%)	58 (64.4%)
Prenatal follow-up, n (%)	77 (85.6%)
Preeclampsia, n (%)	9 (10%)
Gestational diabetes mellitus, n (%)	3 (3.3%)
PPROM, n (%)	13 (14.4%)
PPROM: Prolonged premature rupture of membranes.	

**Table 2. Demographic and clinical features of the patients**

Birth weight, mean ± SD, g	1005 ± 290
Gestational age, mean ± SD, wk	27.3 ± 2.3
Male gender, n (%)	55 (61%)
Surfactant therapy, n (%)	65 (72.2%)
Supplemental O <sub>2</sub> on 21 <sup>th</sup> day, n (%)	87 (95.5%)
Supplemental O <sub>2</sub> on 36 <sup>th</sup> wk, n (%)	33 (36.7%)

(35.5%) infants who needed respiratory support as mechanical ventilation or nasal CPAP received rescue hydrocortisone treatment after 3<sup>rd</sup> week of life whereas 58 (64.4%) infants who were beyond 36<sup>th</sup> postmenstrual week and on oxygen and/or pressure support received treatment for BPD.

Mean duration of hospitalization was 79.5 ± 24.4 days and mean initiation time of hydrocortisone was 41.8 ± 20.1 days. The effect of hydrocortisone treatment on respiratory support is shown in Table 3. Mean duration of hydrocortisone treatment was 22.5 ± 14 days. After treatment only 3 (3.4%) patients were still on respiratory support. Three patients who did not respond to hydrocortisone received dexamethasone for extubation. Overall, 15 (16.6%) infants were discharged with home oxygen despite the hydrocortisone or dexamethasone treatment (Table 3).

When safety of the drug was evaluated 8 (8.8%) infants had early complications of hydrocortisone treatment such as hypertension (2), cardiomyopathy (3) and sepsis (3). Neurodevelopmental outcomes are summarized in Table 4.

## DISCUSSION

The aims of this study were to investigate whether hydrocortisone was safe and efficacious for extubation of very low birth weight infants who still needed pressure support beyond third week of life, and whether it

**Table 3. The efficacy of hydrocortisone in weaning of supportive respiratory therapy**

	Before HC	After HC
Supplemental O <sub>2</sub> , n	87	15
nCPAP, n	13	-
Mechanical ventilator, n	15	3
O <sub>2</sub> free survival, n	-	69
HC: Hydrocortisone.		

**Table 4. Neurodevelopmental outcomes**

**Subjects with follow-up data, n 37**

Neurosensory abnormality	
Any CP, n (%) <sup>a</sup>	5 (13.5%)
Disabling CP, (%) <sup>b</sup>	2 (5.5%)
Bilateral blindness, n (%)	0 (0)
Bilateral deafness, n (%)	0 (0)
MDI n 37	
Mean ± SD	93.4 ± 19.2
70-84, n (%)	5 (13.5%)
≥ 85, n (%)	25 (67.5%)
PDI n 37	
Mean ± SD	80.5 ± 22.6
< 70, n (%)	15 (40.5%)
70-84, n (%)	7 (19%)
≥ 85, n (%)	15 (40.5%)

Mild, moderate or severe cerebral palsy.

Disabling CP, Bilateral blindness, or bilateral deafness requiring amplification.

MDI: Mental development index.

PDI: Psychomotor development index.

altered progress of BPD. This study shows that hydrocortisone is a potent in reducing supplemental oxygen and ventilator dependency. It further provides evidence that acute side effects, related to neonatal glucocorticoid therapy are scarce and acceptable.

The use of oral and intravenous steroids has been studied extensively in infants with BPD. There is a little doubt that when administered early and moderately early, they facilitate weaning from mechanical ventilation and extubation. Since the use of dexamethasone in preterm very low birth weight infants to prevent BPD has not been recommended any longer because of the obvious increases in neurologic complications, there is an increased tendency towards to use different types of steroids which is thought to be safer such as hydrocortisone (11).

Doyle et al. reported a systematic review and meta-analysis of the RCTs of hydrocortisone in preterm neonates and identified a total of eight trials (11). In all of these studies hydrocortisone was started in the first week of life before BPD was established. In all except one study the dose of hydrocortisone was as 1 mg/kg and they concluded that there was no evidence to support the use of hydrocortisone to prevent BPD. On contrary, we demonstrated that hydrocortisone at 1 mg/kg dose was effective to wean patients from respiratory support

in patients who progress to BPD or had BPD. Reports of hydrocortisone therapy given to facilitate extubation have been limited to cohort studies. In the first reported study, 25 infants treated with hydrocortisone at one hospital (5 mg/kg per day, tapered over three weeks) were compared with 25 untreated infants at the same hospital and additionally with a cohort of 23 infants treated with dexamethasone (0.5 mg/kg per day, tapered over three weeks) at a separate hospital (12). The investigators found that hydrocortisone was an effective as dexamethasone in weaning infants from the ventilator and in decreasing supplemental oxygen therapy, with fewer short-term adverse effects. Follow-up of these children at school age revealed no differences in neurodevelopmental outcomes between their comparison groups whereas dexamethasone treated infants more often had an abnormal neurologic examination and less favorable school performance than their comparison cohort. Although we also demonstrated high success rate of hydrocortisone in facilitating extubation, being observational study neurodevelopment results of our patients could only give idea about our cohort. Compared with preterm infants not treated with hydrocortisone, no differences have been found in neurocognitive or motor outcome, or in the incidence of brain abnormalities on magnetic resonance imaging, after hydrocortisone treatment for bronchopulmonary dysplasia in long-term follow-up studies at 5-8 years of age (6,7,13-15), besides hydrocortisone treated children were younger, smaller and sicker than their untreated comparison group. Importantly these children were treated exclusively with hydrocortisone and there was no contamination by later prescription of dexamethasone. However, the patient population was retrospectively enrolled and hydrocortisone administration did not commence until after the first postnatal week. Waterberg et al. and Peltoniemi et al. used early hydrocortisone treatment and both reported no adverse effects on neurodevelopmental outcomes at 18 to 22 months' corrected age (16,17).

Potential complications of prolonged corticosteroid therapy include infection, hypertension, hyperglycemia, adrenocortical suppression, somatic and lung growth suppression, hypertrophic cardiomyopathy and gastrointestinal catastrophes' such as bleeding, perforation and necrotizing enterocolitis. In this study we observed some side effects including, hypertension (n= 2), hypertrophic cardiomyopathy (n= 3) and infection (n= 3) but the other mentioned side effects did not occur in the patient cohort. In two early treatment (prophylactic) hydrocortisone studies, enrolment was stopped because of an increased incidence of sponta-

neous gastrointestinal perforation with combined hydrocortisone-indomethacin treatment (18,19). In very low birth weight infants, low-dose hydrocortisone alone (in the absence of co-treatment with prophylactic indomethacin) did not lead to gastrointestinal perforation. More studies are needed to examine the type and safe dose of corticosteroid in weaning patients from respiratory support and treatment of BPD. To our knowledge this study is unique in the literature along with the hydrocortisone dose and the initiation time. Since present study was an observational one, our results should provide some guidance for the late use of hydrocortisone in infants with BPD. There is a need for prospective randomized controlled trials which will verify the effectiveness and safety of this practice.

#### CONFLICT of INTEREST

None declared.

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