Diffuse Neonatal Hemangiomatosis with Unilateral Cranial Nerve Palsy Improved by Propranolol

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ABSTRACT

Diffuse neonatal hemangiomatosis (DNH) is characterized by multiple capillary or cavernous hemangiomas on the skin and internal organs occurring during the neonatal period. It is a life-threatening condition due to high-output heart failure with a mortality rate of 60-85% without proper treatment. The areas that are most commonly involved include the skin (100%), liver (64-100%), and central nervous system (52%). Corticosteroids are the drugs of choice as an initial treatment and have a response rate of 30-60%. We present here a case of a newborn baby with multiple hemangiomas on her skin (scalp, lips, neck, back, shoulder, arm, buttock, and leg), brain (right cerebellum, pons, and medulla oblongata), lungs, liver, kidney, and bones. She suffered from 6th, 7th, 9th, 10th, and 12th cranial nerve palsy resulting from hemorrhage of the hemangiomas in the brain. The first-line treatment of prednisolone (4 mg/kg/day) was not effective and propranolol (2 mg/kg/day) was administered as a second-line treatment. After 2 weeks of treatment, the hemangiomas had decreased in size with no associated acute hemorrhage. The infant is now 10 months old and both the multiple hemangiomas and cranial nerve palsy have improved. Propranolol was effective without significant adverse effects in treating DNH resistant to corticosteroids.

Key Words: Abducens nerve palsy, Facial palsy, Hemangioma, Propranolol

INTRODUCTION

Diffuse neonatal hemangiomatosis (DNH) is a rare and fatal disorder characterized by multiple cutaneous and visceral hemangiomas at birth or during the neonatal period¹⁾. The areas most commonly involved with visceral hemangiomas are the liver (64-100%), central nervous system (52%), respiratory tract, and gastrointestinal tract²⁾. The condition is life-threatening with a mortality rate of 60-85% without appropriate treatment. Causes of death include high-output heart failure caused by a high-flow hepatic hemangioma with a large shunt, extensive bleeding of a hemangioma, hepatic failure, or disseminated intravascular coagulopathy in which platelets and clotting factors are activated within the hemangiomas²⁾. Corticosteroids are the first drug of choice; however, the response rate is

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just 30-60%³⁾. There have been numerous case reports of DNH treated with interferon-alpha, vincristine, cyclophosphamide, or propranolol as a second-line treatment when patients were refractory to first-line corticosteroid treatment^{1,3-5)}. However, the response rates, adverse effects, dosages, and durations of second-line treatments for DNH are not yet clearly defined owing to a lack of prospective, randomized, controlled studies. We present here a case of a newborn baby with multiple hemangiomas in her skin (including the scalp, lips, neck, back, shoulder, arm, buttock, and leg), brain (right cerebellum, pons, and medulla oblongata), lungs, liver, and kidney. She also suffered from 6th, 7th, 9th, 10th, and 12th cranial nerve palsy caused by hemorrhaging hemangiomas in the brain. Prednisolone as a first-line treatment was not effective, whereas propranolol as a second-line treatment was effective without significant adverse effects. With propranolol, the size of her hemangiomas decreased and her cranial nerve palsy improved.

CASE REPORT

A 1-day-old baby girl was transferred to our neonatal intensive care unit with multiple red cutaneous lesions. She was born at a gestational age of 38 weeks and 4 days by cesarean section due to fetal distress. Her mother and father were 25 and 28 years old,

respectively. Her mother's obstetric history was gravida 1, para 0. Prenatal ultrasonography revealed no fetal abnormalities; no significant events occurred during the pregnancy; and there were no maternal complications associated with the pregnancy. The baby's blood pressure was 61/32 mmHg; body temperature, 35.4 °C; and heart rate, 129 beats per minute. Her body weight was 2,530 g (10th to 25th percentile); height, 45 cm (10th to 25th percentile); and head circumference, 33.5 cm (50th to 75th percentile). Her skin lesions were purpuric to cherry-red in color and she was diagnosed as having more than nine multiple cutaneous hemangiomas on her scalp, lips, neck, back, shoulder, arm, buttock, and leg (Figures 1A, 1B). Their diameters varied from 2 to over 10 mm, and they were friable by friction; when she sucked the nipple of her milk bottle, the hemangioma on her lip tore and bled.

On the 5th postnatal day, she could not form any expressions on the right side of her face or close her right eye and the lateral gaze in her right eye was impaired. She developed hoarseness and an impaired gag reflex, suggesting unilateral 6th, 7th, 9th, 10th, and 12th cranial nerve palsy (Figure 1C). Brain magnetic resonance imaging revealed acute hemorrhage at the right cerebellum, pons, both medial temporal lobes, and the medulla oblongata (Figure 2A). Her prothrombin and activated partial thromboplastin times were normal at 12.6 (INR 1.20) and 42.6 seconds, respectively.

The baby had no cardiac defects with a 70% ejection fraction on echocardiogram. On chest computed tomography (CT), three hypervascular lung masses were observed in the left upper lobe, the posterior segment of the right upper lobe, and on the lateral side of the right lower lobe suggesting hemangiomas (Figure 2B). Abdominal CT showed a 17×17 mm hypervascular mass between the branch of the S3 portal vein and the left hepatic vein in the liver, while multiple variable-sized mass lesions in the left kidney further suggested hemangiomas (Figure 2C). In addition, plain radiographs showed radiolucent bony lesions suggesting hemangiomas at the anterior arc of the left 1st rib, the proximal metaphysis of the right humerus and left tibia, and at the distal metaphysis of the left femur.

We initiated treatment with oral prednisolone (4 mg/kg/day) from the 27th through the 55th postnatal days for a total duration of 4 weeks; however, no clinical response was observed. Therefore, oral propranolol (2 mg/kg/day) was administered as a second-line treatment and no significant adverse effects; such as hypoglycemia, bradycardia, hypotension, and so for-

Figure 1. (A) 1.5×1.5 cm cherry-red mass on the infant's upper lip, (B) two cherry-red masses on her right upper arm. (C) On the 5th postnatal day, she could not form any expressions on the right side of her face or close her right eye. In addition, her lateral gaze in the right eye was impaired.

th; were observed. After two weeks of treatment, the size of the hemangiomas had decreased, their color had changed from red to blue/purple, and the infant's cranial nerve palsy had improved. She was discharged with oral propranolol and followed up in the out-patient department.

After 4 months of propranolol treatment, the cutaneous hemangiomas located on her scalp, lips, neck, back, shoulder, arm, buttock, and leg were diminished. On follow-up radiographic studies, the multiple brain hemangiomas had decreased in size and number (Figure 3A), the hemangiomas on the lungs had disappeared (Figure 3B), and the hemangioma on the left kidney had decreased in size (Figure 3C). On plain radiographs, the sizes and numbers of multiple radiolucent bony lesions that suggestive of hemangiomas had also decreased. The hepatic hemangioma persisted and did not decrease in size and no heart failure was found on the follow-up echocardiogram. The baby is now 10 months old and her cranial nerve palsy has improved (Figure 4). She is able to form facial expressions and does not exhibit hoarseness or an impaired gag reflex. However, the 6th nerve palsy remains and the lateral gaze of her right eye is

impaired. She is able to make vowel sounds, crawl, and sit alone without support.

DISCUSSION

DNH is a rare condition and there have been only six reported cases in Korea⁶⁻¹¹. A treatment with a corticosteroid was effective in just one Korean case⁷, and the remaining five were found to be refractory to the usual corticosteroids⁸. In those cases, the hemangiomas improved by treatment with prednisolone concomitant with interferon-alpha, vincristine, or high-dose methylprednisolone pulse therapy.

Corticosteroids are considered as the first-line treatment for DNH. Hemangiomas proliferate from birth onwards and can cause obstruction, massive bleeding, ulceration, or infection of vital organs, which may ultimately be fatal. Thus, early treatment with 2-3 mg/kg/day of the corticosteroid of choice is critical¹². However, the response rate to corticosteroids is just 30-60% and their long-term use causes adverse effects such as restricted

Figure 2. (A) Brain magnetic resonance imaging shows acute hemorrhage of the hemangiomas at the right cerebellum (arrow) and pons (arrowhead), both medial temporal lobes, and the medulla oblongata on gradient echo imaging. (B) Chest computed tomography (CT) shows hypervascular lung masses in the posterior segment of the right (arrow) and left (arrowhead) upper lobes, suggesting hemangiomas. (C) Abdominal CT shows a small hypervascular mass in the left kidney suggesting hemangioma.

Figure 3. (A) The hemangiomas on the right cerebellum (arrow) and pons (arrowhead) were decreased in size on gradient echo imaging. (B) The hemangiomas on the lungs had disappeared on chest computed tomography (CT). (C) The hemangioma on the left kidney was decreased in size on abdominal CT.

Figure 4. At 10 months old, the baby could form facial expressions. However, 6th nerve palsy still remains and the lateral gaze of her right eye is impaired.

growth, poor weight gain, cushing syndrome, adrenal insufficiency, glucose intolerance, gastritis or gastric ulcers, and more¹³. Furthermore, the occurrence of rebound growth of hemangiomas after cessation of corticosteroids is as high as 36%¹².

As a result, newer second-line treatments that are both more effective and well-tolerated over long-term use are needed. There have been numerous studies investigating the use of interferon-alpha, vincristine, cyclophosphamide, and propranolol as second-line treatments for DNH patients refractory to corticosteroid treatment. Interferon-alpha was shown to be effective in treating neonatal hemangioma complicated with consumptive coagulopathy refractory to corticosteroids by inhibiting the proliferation of endothelial cells and angiogenesis¹⁴. The adverse effects of interferon-alpha include neutropenia, anemia, neurotoxicity, elevated liver enzyme levels, and thyroid dysfunction^{3,14,15}. Vincristine, a cancer chemotherapy agent, was also shown to be effective in treating DNH refractory to corticosteroids by inhibiting cell mitosis in the metaphase, interfering with tubulin polymerization, and provoking cellular apoptosis^{4,16}. The adverse effects of vincristine include neurotoxicity, spastic diplegia, and hair loss^{4,16}. Cyclophosphamide has been used as a rescue treatment for life-threatening DNH¹. While it was shown to be effective, it can cause hemorrhagic cystitis, cardiomyopathy, pulmonary fibrosis, and secondary malignancy^{1,17}.

Propranolol, a nonselective beta-adrenergic blocker (class 2 antiarrhythmic), is commonly used for the treatment of hypertension or arrhythmia. It is generally used as a second-line treat-

ment following corticosteroids¹⁸; however, in some intensive care units, it is used as a first-line treatment. In one prospective study, 31 newborn patients with infantile hemangioma were treated with 3 mg/kg/day of propranolol as an initial treatment and this was shown to be effective without significant adverse effects¹⁸. The rapid proliferation of the hemangiomas ceased and then regressed in all patients. The response to propranolol is more rapid than that to corticosteroids, usually 14 days; however, some studies have reported a response up to 8 months after treatment¹⁸. Propranolol down-regulates angiogenetic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) by blocking beta-adrenoceptors^{19,20}. It also induces vasoconstriction by decreasing nitric oxide and enhances apoptosis of endothelial cells, resulting in the regression of hemangiomas. Adverse effects such as bradycardia, hypotension, bronchospasm, and hypoglycemia can occur. While this is very rare in newborn or young infants, cardiovascular checks such as pulse rate, blood pressure, electrocardiograms, and echocardiograms are needed prior to the initiation of propranolol treatment^{5,19}.

The adequate dosage and optimal duration of propranolol administration in neonates are not yet clearly defined and remain uncertain due to a lack of prospective, randomized, controlled studies. Sufficiently long treatment periods are required to prevent rebound growth of hemangiomas in vital organs. Thus, the recommended duration of propranolol treatment is approximately 7 months as DNH may continue to proliferate for a period of time after birth and after pro-apoptotic components become predominant¹⁹.

In conclusion, we present here a case of a patient with DNH with cranial nerve palsy refractory to a corticosteroid in whom propranolol was effective without significant adverse effects. Propranolol can be considered as a first-line rescue treatment in life-threatening cases of DNH. Additional prospective, randomized, controlled studies comparing second-line drugs with corticosteroids are required, although the implementation of such studies will be difficult, owing to the rarity of this condition.

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