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Pulmonary hypertensive crisis following ethanol sclerotherapy for a complex vascular malformation

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Abstract

Anhydrous ethanol is a commonly used sclerotic agent for treating vascular malformations. We describe the case of a full-term 15-day-old female with a complex venolymphatic malformation involving the face and orbit. During treatment of the lesion with ethanol sclerotherapy, she suffered acute pulmonary hypertensive crisis. We discuss the pathophysiology of pulmonary hypertension related to ethanol sclerotherapy, and propose that hemolysis plays a significant role. Recommendations for evaluation, monitoring and management of this complication are also discussed.

INTRODUCTION

The options for treating vascular malformations in infants and children are limited by the size of the child and the location of the lesion. Surgery is associated with high rates of recurrence, and recurrent lesions are often more difficult to treat. Treatment options include medical therapies such as sirolimus and sildenafil, both investigational. Sclerotherapy is usually considered first-line treatment, and ethanol has emerged as the agent of choice because of its effectiveness and low cost.¹ The sclerotic action of ethanol is due to a direct cytotoxic effect on endothelial cells by disrupting cell membranes, it also denatures plasma proteins and induces formation of thrombi.¹

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

With ethanol sclerotherapy, local or minor complications such as blistering, pain, edema, scarring and neuropathy are reported in 10 to 50% of cases.^{1,2} Hemoglobinuria rates of 8 to 34% have been reported.^{1,2} Serious but rare cardiovascular complications have also been documented: hypotension, pulmonary edema, hypoxia and acute pulmonary hypertension with right heart failure (Table 1). Although several possible mechanisms have been proposed, the pathophysiology of these complications has not been established. We discuss the possible role of hemolysis and nitric oxide depletion in the development of acute pulmonary hypertension.

CASE

Our patient is a full-term female born to a G2 mother after an uncomplicated pregnancy. At birth, a large vascular mass was noted to involve her left orbit, causing severe proptosis (Figure 1a). A magnetic resonance scan of the face, neck and orbit demonstrated a complex cystic and solid lesion thought to be a combined venolymphatic malformation with three principle compartments.

The multidisciplinary Vascular Malformation team was consulted. Surgery was thought to be risky and palliative at best. Medical therapy was initiated with sildenafil, but there was no improvement after a week. Due to concerns for the development of amblyopia, the decision was made to pursue an interventional radiology procedure.

On the day of the procedure, she was 15 days old and weighed 3.4 kg. She was hemodynamically stable, breathing room air, and had no medical issues other than her vascular lesion. General anesthesia and intubation were performed before the procedure. High-resolution venography was done prior to the procedure finding no major venous outlets that could not be occluded by external compression.

Over the next 20 min, anhydrous ethanol was administered, a total of 2 ml of ethanol were injected into and fully aspirated from the lateral compartment, a purely macrocystic lymphatic malformation. The infraorbital and a superior orbital compartment both demonstrated venous communication. A total of 3 ml of anhydrous ethanol were injected into the infraorbital compartment, and 2 ml into the superior orbital compartment. Each small aliquot was aspirated prior to the next instillation, as blood and lymph were also aspirated it was not possible to measure exactly how much ethanol remained intralesional, but the intention was to aspirate the full volume that was injected. After completing the administration, in order to displace and dilute any ethanol left in the lesion while still under anesthesia and in a controlled environment, the tissues were massaged gently to express any latent ethanol, at which point there was acute clinical decompensation.

Oxygen saturation decreased to 80%, heart rate increased to 200 beats/min, and the mean arterial blood pressure decreased to 30 mm Hg. Manual ventilation was initiated, the endotracheal tube was suctioned, tube position and anesthetic depth were confirmed, additional muscle relaxant was given, and albuterol was administered. Due to concern for impending cardiovascular collapse, epinephrine boluses were given, resulting in transient improvements in oxygenation, airway resistance and perfusion. Dexamethasone and diphenhydramine were also given for the possibility of an allergic reaction. The infant was

transported to the neonatal intensive care unit (NICU) for further evaluation and management.

In the NICU, echocardiogram revealed severe right ventricular (RV) dilation, RV systolic pressure 45 mm Hg above right atrial pressure, right to left shunting across a patent foramen ovale and decreased biventricular function. There was no evidence of emboli. Inhaled nitric oxide (iNO) was started at 20 p.p.m., and epinephrine was administered as a continuous infusion.

Her hemoglobin was 5.1 g dl⁻¹ (decreased from 11.3 g dl⁻¹ prior to the procedure), glucose was 455 mg dl⁻¹ and urinalysis revealed hemoglobinuria. Arterial blood gas demonstrated a metabolic acidosis with a bicarbonate of 12 mmol l⁻¹. Fluid resuscitation included 20 ml kg⁻¹ packed red blood cells and 10 ml kg⁻¹ fresh-frozen plasma.

An ethanol level 5-h post-procedure was 37 mg dl⁻¹. Though data are lacking on alcohol metabolism in infants, reports suggest increased metabolism in children compared to non-alcoholic adults, with rates of 28 to 41 mg dl⁻¹ h⁻¹.^{3,4} Based on a metabolic rate of 28 mg dl⁻¹ h⁻¹ and assuming zero-order kinetics, we estimate an initial ethanol level of 177 mg dl⁻¹.

Following fluid resuscitation and initiation of iNO, her clinical condition stabilized, the epinephrine drip was weaned off over 7 h. iNO was weaned and discontinued after 36 h, and she was extubated shortly thereafter. Repeat echocardiogram 4 days following the procedure showed normalized RV pressure and improved biventricular function. She was discharged 7 days following the procedure.

DISCUSSION

At the time of our patient's acute decompensation, several possible explanations were considered: chemically-induced bronchospasm, anaphylactic reaction, pulmonary embolism, airway obstruction and systemic ethanol absorption. The acute onset of instability related to the massage of latent ethanol and the elevated serum ethanol level suggest ethanol was the causative factor.

Proposed mechanisms of ethanol-induced cardiovascular collapse include a direct cardiac depressant effect, vasodilator effect of ethanol and ethanol-induced pulmonary vasoconstriction.⁵⁻⁷ The cause of pulmonary vasoconstriction has not been established. Speculations include endogenous catecholamine release, platelet destruction with thrombus formation and prostaglandin release.^{6,7}

Ethanol causes hemolysis by affecting red blood cell membrane integrity and promoting aggregation of intrinsic proteins.⁸ We propose that ethanol-induced intravascular hemolysis contributes to the development of pulmonary vasoconstriction—via depletion of nitric oxide.

A significant decrease in haptoglobin (a plasma glycoprotein that binds extra-corpuscular hemoglobin) during ethanol sclerotherapy for venous malformations has been reported.² In the setting of acute intravascular hemolysis, the binding capacity of haptoglobin is overwhelmed, leading to increased free plasma hemoglobin. Plasma hemoglobin consumes

nitric oxide in a fast, irreversible reaction that produces nitrate. Even a small amount of free hemoglobin can completely inhibit endothelial nitric oxide and cause endothelial dysfunction.⁹

The combination of nitric oxide depletion and other vasoconstrictive stimuli such as hypoxia, hypercapnia and sympathetic surge can contribute to even greater increases in pulmonary pressure and serious cardiovascular effects.

The reported incidence of pulmonary hypertension during ethanol sclerotherapy ranges from 24 to 30%, but the true incidence may be higher, as it may be under-recognized in the absence of invasive monitoring to measure pulmonary arterial pressure (PAP).^{10,11}

Clinically, an intravascular ethanol dose of 1 ml kg⁻¹ is considered safe.² Although our patient received a total dose of 7 ml of ethanol (2 ml kg⁻¹), because only 5 ml was injected into the venous components of the malformation and much of the injected ethanol was aspirated, we estimate her total intravascular dose as approximately 1 ml kg⁻¹.

Direct monitoring of PAP is invasive, and not likely to be employed in routine practice. Therefore, recognition of pulmonary hypertension relies on the index of suspicion and vigilance of the clinical team, availability of intraoperative echocardiogram would aid in diagnosis. Prior to the procedure, if the patient is on sildenafil for the lesion, it may be prudent to continue the medication. During the procedure, attempts should be made to avoid stimulating pulmonary hypertension by maintaining adequate sedation/anesthesia and promoting hyperoxia and mild hyperventilation. The ability to administer nitric oxide should be available. Availability of appropriate personnel must also be considered when scheduling sclerotherapy procedures.

Our patient made a full recovery with no long-term sequelae; her vascular malformation continues to improve (Figure 1b).

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Figure 1.

(a) Large orbito-facial venolymphatic malformation prior to sclerotherapy. (b) Venolymphatic malformation 3 months after ethanol sclerotherapy.

Table 1

Major complications associated with ethanol sclerotherapy

Procedure	Age	Ethanol dose	Complication
Venous malformation sclerotherapy	21 years	35 ml of ethanol (0.52 ml kg ⁻¹)	Hypotension, bradycardia Diffuse alteration in cardiac contraction Death ^{a5}
Vascular malformation	Not specified	Not specified	Tachypnea, hypoxia, pulmonary edema Death ^{b12}
Vertebral hemangioma	32 years	10 ml 100% ethanol	Bradycardia, apnea, asystole ¹³
Vascular malformation	16 years	1 ml kg ⁻¹	Bronchospasm, unilateral pulmonary edema, right heart failure, hemolysis ²
Vascular malformation	11 years	40 ml mixture (0.85 g ethanol per kg)	Tachypnea, hypoxia, bradycardia, hypotension, right ventricular dysfunction, pulmonary hypertension ¹⁴
Lymphatic malformation	Neonate	Not specified	Hypotension ¹⁵
Vertebral hemangioma (11 cases)	10-36 years	8-10 ml	Hypotension, bradycardia ¹⁶

^aNo evidence of embolism or macroscopic abnormalities of heart and lungs on autopsy.^bLung pathology: acute vasculitis and capillaritis.