Perinatal/Neonatal Case Presentation

Resolution of Peripheral Artery Catheter-induced Ischemic Injury Following Prolonged Treatment with Topical Nitroglycerin Ointment in a Newborn: A Case Report

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Tissue ischemia, necrosis, and gangrene are uncommon but well-described complications of arterial catheterization in the neonate. Treatment options for progressive tissue necrosis following arterial embolization and/or vasospasm are limited in these patients secondary to unpredictable pharmacokinetics and risks associated with systemic anticoagulation or vasodilatation in newborns. We report a case of a multidose regimen of topical 2% nitroglycerin ointment for reversing severe tissue ischemia following peripheral arterial line placement. The favorable response in this infant suggests that topical nitroglycerin therapy should be considered as potential therapy to ameliorate the effects of vascular compromise following arterial line placement in neonates.

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INTRODUCTION

One of the more serious complications of arterial catheterization is the obstruction of blood flow from thrombi, emboli, or vasospasm causing tissue ischemia.[1–5] If end arteries are obstructed, a series of changes have been described: the affected area becomes pale, cyanotic, cool, and motionless with absent pulses.[1,5] This sequence may result in significant loss of cutaneous, subcutaneous, muscle, and other tissues. The standard intervention is to remove the catheter and evaluate peripheral circulation for further treatment. Deep arterial or venous (pulmonary/renal) thrombotic complications are typically treated with heparin or thrombolytic agents. However, the use of heparin in preterm infants (for treating peripheral thrombi) has been considered hazardous because of potential hemorrhagic complications, specifically intraventricular hemorrhage (IVH). Currently, no standard approach exists for treating small clots in the distal extremities in these infants. Nearly a decade ago, several case reports of reversing severe tissue ischemia from thrombus or vasospasm in the neonatal population with one to three applications of topical nitroglycerin ointment were reported.[4] To our knowledge, we are reporting the first successful treatment of severe tissue ischemia with topical 2% nitroglycerin ointment over an extended period (27 days) until complete clinical recovery from tissue ischemia was achieved.

CASE REPORT

Baby girl D was an 896-g infant born at 26 weeks' gestation to a 23-year-old mother, gravida 1, para 0. Delivery was by emergency C-section secondary to placental abruption. APGAR scores were 2, 6, and 7 at 1, 5, and 10 minutes, respectively. The infant was intubated and received surfactant in the delivery room. The physical examination on admission showed, clinical hypovolemia, with delayed capillary refill (>3 seconds), hypotension with a mean blood pressure of 15 to 20 mmHg and anemia. An umbilical venous line was placed, and two slow normal saline boluses (10 ml/kg) were administered at 1 and 2 hours of life with some improvement, a dopamine drip was started at 10 mcg/kg/minute by 3.5 hours of life and a transfusion of 10 ml/kg of packed red blood cells was given. Mean blood pressure increased to 25 to 30 mmHg around 8 hours of life and then remained stable.

Since the attempt to insert an umbilical arterial line was unsuccessful, a peripheral arterial line was placed at 30 minutes of life. The left hand distal to the insertion site was noted, 45 minutes after the procedure, to be cool and pale with cyanotic discoloration extending from the mid-palm to the fingertips (Figure 1). The catheter was immediately removed. The skin was grossly intact and capillary refill was delayed. A provisional diagnosis of tissue ischemia was made and confirmed by a Doppler flow study at 18 hours of life. In an attempt to negate the peripheral vasoconstrictive effects of dopamine and maintain perfusion, dobutamine at 10 mcg/kg/minute was added by 10 hours of life, and dopamine was weaned and finally discontinued at 42 hours of life. Anticoagulation was considered as one possible strategy to preserve perfusion and prevent loss of the fingers and distal hand,

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Figure 1. Ischemia of fingers before initiation of treatment.

Figure 2. Left hand after completion of treatment.

but the risks of heparinization were considered unacceptable in this extremely preterm infant.

After blood pressure and peripheral perfusion had normalized at 8 hours of age, a ribbon of 2% nitroglycerin ointment (less than 4 mm/kg) was sparingly applied to the forearm, approximately 1 cm proximal to the line of pallor. Remarkable improvement in color and perfusion was noted in the palm over the next 8 hours. Subsequent doses were applied every 8 hours approximately 1 cm proximal to the site of ischemia following the anatomic course of the arterial supply.

Overall, the clinical status of the infant was stable. She remained intubated on SIMV for approximately 48 hours with a mean airway pressure of 7 to 8 cm H_2O and fraction of inspired oxygen of 21%. Ampicillin and gentamicin were discontinued at 72 hours with a negative blood culture result. Head ultrasound findings were normal on day of life 133.

There was gradual improvement in color and capillary refill over the next 2 weeks. By day 12, the area of ischemia was limited from the base to the tips of fingers two through five. The ointment application was advanced progressively towards the left palm between the third and fourth fingers to carry the nitroglycerin ointment through collateral circulation. This strategy was successful and on day of life 18, the ischemia was localized to the tips of the fingers. After a 27-day regimen, the nitroglycerin ointment was discontinued. The nail beds were intact with full restorative function of the hand (Figure 2). A 8 months after the initial insult, the exam showed no noticeable deficits and fingertips remained pink.

DISCUSSION

Tissue ischemia, resulting from embolization and/or vasospasm, is a known complication of arterial catheterization. When the vascular endothelium is injured from arterial catheters, the intimae of the vessel wall responds by eliciting an inflammatory response leading to local hemostasis and formation of a thrombus that can restrict blood flow and causes tissue ischemia.[4,5] Simultaneously, platelets can adhere to exposed collagen and other subendothelial tissues, releasing potent vasoconstrictors that contribute to vasospasm, occlusion, and tissue ischemia. Therefore, thrombosis and vasospasm are closely inter-related, and both may respond to therapies, like topical nitroglycerin, that cause vasodilatation and increased blood flow.

The primary pharmacological effect of nitroglycerin is a relaxation of vascular smooth muscle, resulting in the dilation of both arterial and venous beds, counteracting the vasoconstriction from platelet aggregation. In the smooth muscle cell, nitroglycerin is converted to nitrite ions and later to nitric oxide, activating guanylate cyclase and increasing the cells' cGMP. The elevated cGMP leads to dephosphorylation of the myosin light chain resulting in smooth muscle relaxation.[6] In addition to vasodilatation, nitroglycerin can increase collateral circulation to areas of peripheral ischemia. The amount of nitroglycerin reaching the circulation varies directly with the size of the area of application and the amount of ointment applied. A dose of 4 mm/kg is equivalent to 0.2 to 0.5 μg/kg/minute.[7] In adults, about 1 mg/kg of nitroglycerin would be required before patients manifest clinically significant ($>10\%$) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin would require an even larger dose of nitroglycerin. Therefore, as with any prolonged use of a nitric oxide compound, toxicity remains a concern and the measurement of methemoglobin levels should be considered for future cases.

In adults, the onset of action is approximately 20 to 60 minutes, and the pharmacological effects last 3 to 6 hours. Nitroglycerin ointment is metabolized by the liver, and excreted by the kidney. The known side effects include headache, hypotension, tachycardia, nausea, vomiting, skin irritation, and flushing,[6] although the pharmacokinetics in infants have not been studied.

Nitroglycerin became commercially available as a 2% ointment in 1974 and has been used as a standard treatment for angina in adults. Wheeland et al.[8] have reported successful use of nitroglycerin ointment for improving capillary blood flow because of digital ischemia from digital ulcers in adults. The initial case report of nitroglycerin use in a neonate in 1988[2] was followed by

reports of its use as an aid to the insertion of peripheral venous catheters with unsuccessful results and occurrence of local complications.[9–11] In 1992, Wong et al.[4] reported treatment of four neonates with peripheral tissue ischemia with nitroglycerin ointment. More recently, 0.2% topical nitroglycerin ointment was used to treat ischemia associated with umbilical and radial arterial lines at a lower dose (4 mm/kg) with apparent success and no side effects being observed.[12,13] We report our experience of using 2% nitroglycerin ointment (less than 4 mm/kg) over an extended period of time for reversing tissue ischemia. Although our treatment was successful, nitroglycerin use is not without potentially serious risks such as hypotension and shock in a preterm infant; therefore, the lowest most effective concentration of nitroglycerin must be used in neonates. Currently, there are no standard dosage and administration recommendations for use of this drug in neonates. Therefore, using a diluted concentration of nitroglycerin ointment could be beneficial and needs to be explored. Although it remains impossible to predict whether or not there might have been complete resolution over the 3-week period in this case without the nitroglycerin ointment, we believe that it may have contributed to the favorable outcome.

CONCLUSION

We report a case of tissue ischemia associated with arterial line placement reversed by regimented topical nitroglycerin ointment. As a noninvasive measure, topical nitroglycerin ointment may be a useful therapy over a period of 3 weeks for reversal of tissue ischemia. The most effective dose of nitroglycerin ointment in neonates has not been established. Further investigation regarding concentration and dosage must be done before routine use of nitroglycerin ointment in neonates with distal ischemia can be recommended.

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