

Topical Nitroglycerine Treatment for Sustaining Umbilical Arterial Catheter While Resolving Peripheral Ischemia: A Case Report

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Abstract: Presence of umbilical arterial catheters in extremely low birth weight infants is critical for their management including minimal handling in first few days of life. However, one of the associated risks of indwelling umbilical arterial line is occasional development of peripheral ischemia. In most cases, it invariably leads to discontinuation of the catheter to salvage the ischemic tissue. Discontinuation of the arterial line places the preterm neonate at risk for multiple venipunctures and capillary blood draws and suboptimal hemodynamic monitoring. We report the first case of peripheral ischemia, specifically ischemia of the toes, due to umbilical arterial catheterization in an extremely low birth weight infant [380 grams and 25 weeks gestation secondary to maternal chronic hypertension, preeclampsia, and severe intrauterine growth retardation], where both the umbilical arterial catheter and toes were salvaged by use of topical nitroglycerine ointment. We conclude that topical application of nitroglycerine ointment did not lead to significant hypotension, methemoglobinemia, or intraventricular hemorrhage in this neonate. Currently there are no uniform guidelines regarding the frequency, duration, and safety of nitroglycerin topical administration in the treatment of ischemia in extremely low birth weight infants. A proposal for development of a guideline which should incorporate close blood pressure monitoring, methemoglobin levels, and serial cerebral ultrasounds. This method may help to reduce unnecessary early removal of catheters in the first few days of life, as many neonatal units are moving towards resuscitating peri-viable infants worldwide.

Keywords: Extremely Low Birth Weight Infants, Umbilical Arterial Catheters, Peripheral Ischemia, Methemoglobinemia, Peri-Viable Infants, Intraventricular Hemorrhage

1. Introduction

Umbilical artery cannulation has been reported in medical literature since 1959 [1]. The placement and use of umbilical artery catheters (UAC) and peripheral arterial lines have become routine practice in neonatal intensive care units (NICU) for continuous hemodynamic monitoring and frequent blood sampling thus reducing the need for venipuncture. UACs are imperative in the management of critically ill and peri-viable preterm infants during the first few days of life [2, 3] However, as with most interventions in the NICU, there are associated risks with arterial catheterization including infection, hemorrhage, vascular perforation, and thrombosis [1, 2, 3]. In one recent study, the incidence of arterial ischemia was reported to be around 7%

with increased incidence within lower gestational age groups [4]. Presence of an UAC was one of the major risk factors for arterial ischemia. Most reported problems with presence of the UAC include blanching or cyanosis of extremities that can occur due to vasospasm or embolic incident [3]. Other less commonly associated problems include hematoma, peripheral nerve damage and tissue necrosis [5]. Preterm infants are prone to ischemia due to their vasculature with small arterial diameters and immaturity of hemostasis [6]. Such vascular accidents occur more distally, resulting in an ischemic injury of the back, buttock, and lower extremities. Conventional management of arterial catheter associated peripheral vasospasm involves warming of the contralateral

extremity for reflex vasodilation followed by catheter removal if peripheral cyanosis or blanching continues [1]. However, this is not always successful and tissue necrosis requiring surgical intervention may ensue [1]. There have been multiple case reports since the late 1980s documenting the use of nitroglycerin ointment to reverse tissue ischemia. Topical nitroglycerine is a powerful vasodilator that bioconverts to nitric oxide and relaxes the vascular smooth muscle and hence can reverse arterial ischemic vasospasm in isolated case reports [2, 7-9]. We report the first case of peripheral ischemia, specifically ischemia of the toes, due to umbilical arterial catheterization in an extremely low birth weight (ELBW) infant, where the both the UAC and toes were salvaged by the use of topical nitroglycerine ointment.

2. Case Report

An extremely low birthweight female preterm infant weighing 380 grams was born at 25 weeks gestational age secondary to maternal chronic hypertension, preeclampsia and severe intrauterine growth retardation. Pregnancy was also complicated by chronic renal failure, lupus erythematosus, thrombocytopenia, and anemia. Due to severe preeclampsia, the infant was delivered by cesarean section, with APGAR scores 3, 6 and 7 at 1, 5 and 10 minutes respectively. She was intubated at birth and was given surfactant. Upon admission to the neonatal intensive care unit, a 3.5F single lumen umbilical arterial catheter (UAC) and 3.5F double lumen umbilical venous catheter (UVC) were placed. Hypotension was treated with a normal saline bolus and Dopamine infusion at 5mcg/kg/min. On day of life 5, she was noted to develop bluish discoloration of the distal part of the second to the fourth toe on the right foot. Warming of the contralateral limb and elevation of the affected limb did not help with the peripheral ischemia, and the toes turned black in the next 3 hours. Due to the patient's extremely low birth weight and hemodynamic instability, the decision to leave the UAC was made for the purpose of ongoing hemodynamic monitoring and frequent lab draws. As the ischemia did not improve over the subsequent 12 hours, 2% topical nitroglycerine ointment was applied. Parents were counseled extensively regarding the advantages and disadvantages of leaving the UAC and the use of nitroglycerine paste. One 1.5mm string of ointment was applied just proximal to the ischemic area of all the affected toes every 8 hours. Discoloration improved within 24 hours. However, after 24 hours of starting treatment nitroglycerine paste was held for 12 hours due to mild hypotension and resumed the following day. By DOL 10, the ischemia fully resolved, and the nitroglycerine ointment was discontinued. Serial cranial ultrasound prior to and after nitroglycerine paste ointment did not demonstrate any intraventricular hemorrhage. There was no documented edema of the toes and the right foot. The infant had an eventful course in the NICU needing prolonged ventilation, PDA ligation and was eventually discharged home at 41 weeks corrected gestational age, weighing 2930g.



Figure 1. Initial presentation of ischemia of second and third toes.



Figure 2. Ischemic toes noted on right foot involving 2nd to 5th toes.



Figure 3. Complete resolution of ischemia of toes 2 week later.

3. Discussion

In this case, we demonstrated that umbilical arterial lines can be left in place even in the presence of arterial spasm or thrombosis that has not responded to contralateral limb warming and elevation of the affected limb. This was particularly important in our peri-viable infant due to her ELBW of less than 400 grams and difficult peripheral arterial access for the purpose of hemodynamic monitoring and frequent lab draws. The patient did not sustain any adverse effects including intraventricular hemorrhage nor significant hypotension despite the application of topical nitroglycerin in the first week of life during which the risk of intraventricular hemorrhage is high [10]. Presentation of ischemic injury can vary and include cold extremities, delayed capillary refill, absent of pulses and discoloration [11]. Risk of development of catheter induced thrombosis is higher among infants of mothers with hypertension due to raised level of endothelin-1, which constricts the placental vessels and increases the chance for complications with indwelling catheters [11]. Preterm infants have fragile blood vessels which make them more prone to vasospasm and thrombosis [5]. Pathophysiology of catheter induced ischemia and thrombosis are twofold. The primary delayed coagulation maturity normally does not take place until 6 months of age, and any significant illness may disrupt homeostasis leading to a fall of alpha-2 microglobulin with subsequent thrombosis and ischemia. The placement of UAC causes vascular endothelial damage leading to increased inflammatory cascade by increasing platelet adhesion and aggregation through the release of adenosine diphosphate and thromboxane, resulting in decreased circulating blood flow, thus formation of thrombosis [5]. The common non-pharmacological methods used for arterial vasospasm or thrombosis in the NICU are warming the contralateral limb [12], elevating the affected limb, warming of the opposite extremity if one extremity is involved, warming of the abdomen if both extremities are involved, and removing the catheter if no improvement in perfusion after 10 minutes [11, 4]. However, removal of the catheter does not always result in resolution of ischemic injury [13]. Extended duration of umbilical arterial catheterization was identified as a cause of peripheral arterial ischemia [14-16]. Treatment options that have been reported in the literature are topical hyaluronidase ointment, subcutaneous low molecular weight heparin, tissue plasminogen activator (tPA), tPA with heparin, topical nitroglycerin (NGC), and surgical management [17]. NGC is a well-known smooth muscle relaxant [18, 19]. In transdermal application, the hepatic first by-pass extraction is avoided unlike in the oral form of administration. A plasma half-life of 2-3 minutes has been reported which indicates the existence of an additional extrahepatic mechanism of clearing [20]. Action involves passive diffusion through the stratum corneum which is influenced by skin permeability [21]. Then it is metabolized in erythrocytes and is taken up or metabolized in the blood vessels which is the likely explanation for its very large clearance. [20]. Nitroglycerine

forms free nitric oxide which activates guanylate cyclase, which leads to vasodilation by guanosine 3,5 cyclic monophosphate. The first report in 2001 demonstrated successful resolution of the ischemic changes on the buttock with topical nitroglycerin use. [8]. Kim et al suggested that earlier treatment is more effective than delayed treatment with NGC [4]. Premature infants have thin stratum corneum which has high skin permeability and skin absorption. NGC acts through cGMP5 pathway resulting in vasodilation and improvement of collateral circulation. Plasma concentration of 1 mcg/dL and higher (0.1 to 0.2 micro g/L) has been reported in successful reversal of ischemia [22]. Safe dosage recommended in literature varies for preterm infants. A multidose regime is recommended in many studies rather than a single dose administration [5, 23]. Kim Lee used 2% NGC in a quantity of 4 mm/kg ribbon every 8 hours. The vasodilatory effect can be evident within 15-30 minutes and can last up to 6 hours [4]. Zafarghandy et al reported similar dosage every 6 hours for 2 weeks without major side effects [24]. Vivar et al used a dose of 1.22mg/kg which was 4 mm/kg without significant side effects [12]. Some authors reported success with use of NGC spray. [13, 19]. Mosali et al used 1 spray to the affected part at approximately 2cm proximal to the line of pallor in each affected finger every 6 hours (total of 2 mg/kg/day) [5]. Use of NGC patches also has been reported with resolution of ischemic injury [4, 23]. Many studies have reported improvement of ischemia and circulation after topical NG application. The side effects of NGC include hypotension due to vasodilation, decreased cardiac output due to venous pooling [2], organic nitrates overdose, production of methemoglobinemia leading to increased oxygen requirements in preterm infants and limb edema [19]. Hypotension resolved in a majority of cases without treatment [2, 7-9]. Methemoglobinemia and associated increase in oxygen requirement has been reported in some preterm infants and hence frequent assessment of methemoglobin level is pertinent in this population with topical use of NGC [25]. Not all studies showed success of ischemia reversal with transdermal use of NGC [13, 25, 26]. In those scenarios, use of other agents may become necessary to reverse the ischemia.

4. Conclusion

In conclusion, topical NGC application for the management of peripheral ischemia appears to be a reasonably safe and beneficial intervention resulting in salvaged tissue and continuation of arterial catheterization as in this reported case study. Considering the long-term outcomes of untreated tissue injury, it is difficult to justify omitting the use of this potentially effective therapy with minimal risks. Topical application of NGC in our ELBW patient in first week life did not lead to significant hypotension, methemoglobinemia, and intraventricular hemorrhage. We were able to sustain the umbilical arterial catheter for a few more days to monitor hemodynamic status and avoid heel pricks for blood draws. Currently, there is no uniform guideline regarding the frequency, duration, and safety administration of NGC in the

treatment of ischemia. A proposal of development of such a guideline with close monitoring of blood pressure, methemoglobin levels, and serial of cerebral ultrasounds may be warranted in the future as more units are moving towards resuscitating peri-viable infants worldwide.

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