

Topical nitroglycerin in neonates with tissue injury: A case report and review of the literature

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Peripheral tissue injury is one of the well-described morbidities associated with stays in the neonatal intensive care unit. Despite the potential long-term disability associated with this event, the current available therapeutic options remain very limited. Topical nitroglycerin has emerged as a promising agent for the treatment of tissue injury in infants. The present article includes a review of the currently available evidence on the use of topical nitroglycerin in the neonatal population, and describes a unique case involving successful use of 2% nitroglycerin in the late treatment of prolonged tissue ischemia in a newborn infant.

Key Words: *Infants; Tissue injury; Topical nitroglycerin*

The use of topical nitroglycerin (TNG) ointment for the treatment of peripheral tissue injuries was first described in 1982 in patients with Raynaud's disease (1). Patients randomly assigned to treatment with glyceryl trinitrate ointment showed improvement in the size of ulcers, with significant reduction in the size of ulcers compared with patients randomly assigned to receive placebo. This report, describing the local capillary vasodilatory properties of TNG, initiated a cascade of research investigating the use of TNG for the treatment of adults and infants with iatrogenic tissue injury (2,3).

To date, the evidence supporting TNG therapy in infants with tissue injury of various etiologies is limited to eight reports describing 14 cases. These reports are consistent in describing successful results with minimal or no adverse events (AEs).

Here, we present a unique case of successful use of TNG in a newborn for the late treatment of a peripheral tissue ischemia, and also review the currently available evidence concerning the use of TNG in infants with iatrogenic tissue injury.

CASE PRESENTATION

A male infant was born at 26+4 weeks of gestation to a gravida 3, para 1 woman who experienced preterm premature rupture of membranes four days before delivery. She received antibiotics and two doses of betamethasone. Delivery occurred via emergency Cesarean section due to placental abruption. Apgar scores were 1, 5 and 8 at 1 min, 5 min and 10 min, respectively. A peripheral intravenous catheter (PIVC) was inserted in the left foot at 15 min of age. Shortly after, the infant developed respiratory insufficiency, and was intubated and mechanically ventilated. At 60 min of age, the physical assessment of the infant demonstrated delayed capillary refill, cold

La nitroglycérine topique chez les nouveau-nés ayant des lésions tissulaires : rapport de cas et analyse bibliographique

Les lésions des tissus périphériques font partie des morbidités bien décrites associées à des séjours à l'unité de soins intensifs néonataux. Malgré les invalidités potentielles à long terme qui y sont liées, les possibilités thérapeutiques demeurent très limitées. La nitroglycérine topique a émergé comme un agent prometteur dans le traitement des lésions tissulaires chez les nourrissons. Le présent article contient une analyse des données probantes sur l'utilisation de la nitroglycérine topique dans la population néonatale, ainsi que la description d'un cas unique portant sur l'utilisation réussie de nitroglycérine 2 % dans le traitement tardif d'une ischémie tissulaire prolongée chez un nouveau-né.

extremities and agitation. The baby's initial blood cell count showed a hemoglobin level of 66 g/L; therefore, 15 mL/kg of packed red blood cells was transfused through the left foot PIVC. A cranial ultrasound was requested, which showed right-side grade IV intraventricular hemorrhage. After the initial stabilization, an umbilical venous catheter was inserted and its placement was verified by x-ray. At 4 h of age, the left foot was noted to be puffy and mildly mottled. The proper placement of the PIVC was assessed using easy flushing, and was saline locked and continued to be closely monitored until 36 h of age, when delayed capillary refill and small areas of bruise over the heel of the left foot were noted. The saline-lock PIVC was immediately removed. Doppler ultrasound of the left foot confirmed the presence of tibial and pedal pulses. Plastic surgery was consulted and the diagnosis of an intracutaneous hematoma was made. Conservative management with close follow-up was recommended.

Over the following six days, his left foot showed some minimal improvement; however, on day 8 of life, the capillary refill of the left foot appeared very sluggish, with mottled to purple skin over the toes, sole and most of the dorsum extending to the ankle area (Figure 1). Doppler ultrasonography of the left foot showed absence of both pedal and tibial blood flow, with no evidence of clots in the arteries. The diagnosis of peripheral tissue ischemia secondary to thromboembolic event or, more probably, severe vascular spasm was made. Orthopedic surgery, plastic surgery and cardiovascular surgery teams were consulted. Considering the overall status of the patient as an extremely premature infant, conservative management appeared to be the only available option, with high probability of need for amputation.

For the purpose of multidisciplinary team management, the infant was transferred to a paediatric tertiary care centre. On

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Figure 1) Ischemia of the left foot and toes before initiation of treatment



Figure 2) Left foot after completion of treatment

arrival, a repeat Doppler ultrasound of the foot was performed and confirmed the absence of any arterial flow in the left ankle and left foot. The option of TNG, as a rescue therapy, was discussed with the parents and a 4 mm/kg ribbon of 2% nitroglycerine ointment was applied over the area of the dorsalis pedis and posterior tibialis arteries of the left foot every 6 h. The treatment continued for a 14-day period and the improvement in pulses, colour and capillary refill were monitored very closely. The heart rate, blood pressure and methemoglobin level of the infant were also monitored frequently to assess for potential adverse effects of the TNG therapy. After 24 h of applying TNG, improvement in circulation and colour of the left side of the foot and fifth toe was noticed. Over the next 48 h, there was significant improvement in capillary refill and circulation of the entire foot, and the first and fifth digits. On day 6 of treatment, a repeat Doppler ultrasound showed occlusion of the distal one-third of the peroneal and posterior tibial arteries with development of collateral circulation. By day 8 of treatment, the perfusion of the fourth toe gradually improved, and normalized within the next five days (Figure 2). There was no change in the perfusion of the second and third toes after 14 days of treatment and TNG therapy was, therefore, discontinued. The infant's blood pressure and methemoglobin level remained stable. The follow-up cranial ultrasounds did not show any change from baseline. No other AE was observed during TNG therapy.

DISCUSSION

Peripheral tissue injuries are one of the well-described iatrogenic morbidities associated with intensive care unit stay in newborns. Extravasation of intravenously administered medication, thrombotic or embolic events secondary to intra-arterial catheters, and peripheral vasospasm resulting from vasoactive drugs or improper placement of the catheter are among the reported causes of this highly morbid condition (3-5). Peripheral tissue injuries can potentially lead to complete necrosis and loss of the affected limb.

Aside from conservative measures, the available therapeutic options for the reversal of an established injury are very limited. Thrombolytic and anticoagulation therapies and local infiltration of phentolamine or hyaluronidase are of very limited benefit in the infant population, and their use demands either systemic administration or cutaneous injection (4-6). This has led many of the intensive care unit practitioners to err on the side of caution and rely solely on conservative management, accepting the high risk of long-term morbidity.

The use of TNG as a salvage therapy for peripheral tissue injuries in neonates has been described since 1988 (3). Although the available evidence is limited to sporadic case reports, there is consistency among all reports in subjective or objective improvement of the perfusion of the affected limb following TNG therapy (Table 1). All newborns experienced complete recovery of the injured tissue except one term infant who experienced extensive ischemia of the left leg, foot and toes, and the preterm infant in our report, who probably experienced a prolonged tissue injury before the application of TNG (7). The term infant with extensive ischemia lost a small area at the tip of his left great toe, and our preterm patient lost his second and third toes from a prolonged injury that could have led to a disastrous sequelae and need for a complete foot amputation. Our case is the first report of successful use of TNG for the delayed treatment of peripheral tissue ischemia. Although the extent to which the ischemic insult was advanced before the start of the TNG treatment is unclear, there is a high probability that the injury was initiated within the first few hours after the insertion of the intravascular catheter. This extent of delay in the start of TNG therapy with successful results has not been previously reported.

The data on dosing regimen and AEs of TNG therapy in infants are derived from adult studies. The initial reports on TNG therapy in infants used a wide range of dosing regimens (0.12 mg/kg to 2.5 mg/kg) which were then changed to 4 mm/kg (1.22 mg/kg) in an attempt to avoid systemic vasodilation (4,5,8). The AE profile of TNG is known to be dose related, and is a result of nitroglycerin's vasodilatory effect. Headache, hypotension, dizziness and methemoglobinemia, although uncommon, are among the reported AEs in the adult population (9). Newborns, especially infants of low birth weight, are known to have impaired skin maturity and can experience variable exposure to a topically administered drug (10). Furthermore, autoregulation of the cerebral blood flow can be easily disrupted in premature infants, and any sudden change in hemodynamic status may result in serious AEs (11). This knowledge has resulted in valid concerns regarding the use of TNG in the infant population. To date, there are only two trials available investigating the use of TNG in newborns (8,12). The open trial of use of TNG in facilitating catheter insertion in newborns showed that four of 10 infants (<1500 g) who received a median dose of 0.7 mg/kg experienced a significant drop in their blood pressure (8), and the double-blinded, placebo-controlled trial of 0.1 mg/kg TNG as an aid to the insertion of a PIVC in term and premature infants did not detect any change in the hemodynamic status of the infants randomly assigned to TNG (8,12). Since the use of TNG for rescue therapy of tissue injuries

TABLE 1
Use of topical nitroglycerin in infants: Currently available evidence

First author (reference), year	GA, weeks	PNA, days	Cause of ischemia	Ischemic site	Time, h*	Dose	Time to first effect	Treatment duration	Outcome	Adverse events
O'Reilly (3), 1988	NS	NS	TPN extravasation	Dorsum of the foot	2.5	0.2 mg	NS	1 h	CR*	No
Denkler (4), 1989	34	1	Dopamine extravasation	Left hand to low forearm, left foot to knee	6	13.8 mm/kg [†]	Minutes	1 dose	CR	No
Wong (5), 1992	25	10	Peripheral arterial line	Right hand	2	4 mm/kg	15 min	1 dose	CR	No
	24	40	Peripheral arterial line	Right hand	Within 24 h	4 mm/kg every 8 h	8 h	12 h	CR	↓BP
	31	4	Dopamine extravasation	Forearm, chest, axilla	1	4 mm/kg	15 min	1 dose	CR [‡]	No
	26	15	Dopamine extravasation	Forearm, arm	0.5	4 mm/kg every 8 h	8 h	24 h	CR	↓BP ↑HR
Varughese (13), 2001	33	10	Umbilical artery catheter	Right hip	4	0.4 mg/kg 2 doses	7 h	30 h	CR	↓BP
Baserga (14), 2002	30	1	Umbilical artery catheter	Left leg, penis, scrotum	1	4 mm/kg	30 min	1 dose	CR	No
	25	1	Umbilical artery catheter	Right leg	1.5	4 mm/kg	45 min	1 dose	CR	No
	23	10	Peripheral arterial line	Left hand	1	4 mm/kg	30 min	1 dose	CR	↓BP
Vasquez (6), 2003	26	1	Peripheral arterial line	Left hand	7	4 mm/kg every 8 h	8 h	27 days	CR	No
Maffei (17), 2006	29	1	Central venous catheter	Left arm	0.5	11 mm/kg [§]	1 h	7 days	CR	No
	32	8	Peripheral arterial line stab	Right hand	1	4 mm ² /kg [§]	3 h	4 days	CR	No
Akingbola (7), 2012	31	60	Femoral peripheral arterial line	Left leg, foot and toes	Within 24 h	4 mm/kg every 8 h	24 h	21 days	Loss of tip of the left great toe	Swelling bulla formation [¶]
Samiee-Zafarghandy (present study), 2013	26	1.5	Peripheral intravenous	Left foot	144	4 mm/kg every 6 h	24 h	14 days	Loss of second and third toes	No

*Start time after the tissue injury; [†]1 inch strip of 2% topical nitroglycerin was smeared over the two sites; [‡]Subcutaneous phentolamine was administered with no effect; [§]Triniplas 5 mg/7 cm²; [¶]Tissue plasminogen activator and heparin were coadministered with topical nitroglycerin. ↓ Decrease; ↑ Increase; BP blood pressure; CR complete resolution; GA Gestational age; HR Heart rate; PNA Postnatal age; NS Not specified; TPN Total parenteral nutrition

in infants was first described, four of 14 studied infants experienced a mild decrease in blood pressure. The observed change in blood pressure either resolved spontaneously or responded to an adjustment in the dose of concomitantly administered inotrope. TNG did not need to be discontinued in any of the cases and no other hemodynamic AEs were reported (5,13,14). Erythema, venous dilation and bleeding when TNG was applied for the ease of the insertion of PIV catheter are among other reported AEs associated with the use of TNG (12).

In a recent report describing a term infant with extensive ischemia of the left leg, foot and toe following insertion of a femoral arterial catheter, swelling of the entire leg with thick eschar and bullae formation was associated with the use of 2% TNG. Although the TNG was initially discontinued, it needed to be restarted within 2 h due to the recurrence of ischemic changes. The swelling and skin changes responded to xeroform gauze dressing with complete healing (7). None of the previously reported AEs associated with TNG therapy were observed in our newborn patient.

CONCLUSION

The absence of adequate data regarding the safety of TNG use in infants, although concerning, must be considered in view of its promising role in the salvage therapy of tissue injury. Considering the disastrous long-term outcome of untreated tissue injury, it is difficult to justify the avoidance of this potentially effective therapy in the fear of unknown AEs. Clinicians should maintain a high level of awareness of the potential AEs while using TNG therapy. The hemodynamic status of the infant should be monitored closely and frequently during the treatment period, especially within the first 6 h of administration, when the peak plasma concentration

occurs (15,16). All infants receiving TNG should be monitored daily for the development of methemoglobinemia and a follow-up head ultrasound should also be considered. Considering the infrequency of tissue injury incidents and the difficulty in performing a systematic study, development of a registry may be of utmost value in informing future guidelines for the safe and efficacious use of TNG therapy in the infant population.

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