Topical Nitroglycerin Ointment as Salvage Therapy for Peripheral Tissue Ischemia in Newborn Infants: A Systematic Review

Authors and degrees:
Katelyn Sushko[1] RN, Catherine Litalien[2] MD, Lauren Ferruccio[3] PharmD, Andrea Gilpin[4] PhD, MBA, Maryann Mazer-Amirshahi[5] PharmD MD PhD, Anthony K Chan[6] MBBS, John van den Anker[7,8] MD PhD, Thierry Lacaze-Masmonteil[9] MD PhD, Samira Samiee-Zafarghandy[10] MD

[1] Faculty of Health Sciences, School of Nursing, McMaster University, Hamilton, Ontario, Canada.

[2] Division of General Pediatrics, Department of Pediatrics, and the Rosalind & Morris Goodman Family Pediatric Formulations Centre, Centre Hospitalier Universitaire Sainte-Justine, Université de Montréal, Quebec, Canada.

[3] Department of Pharmacy, Hamilton Health Sciences, Hamilton, Ontario, Canada.

[4] General Manger, Rosalind & Morris Goodman Family Pediatric Formulations Centre, Centre Hospitalier Universitaire Sainte-Justine,

[5] Department of Emergency Medicine, MedStar Washington Hospital Center, Georgetown University School of Medicine, Washington, DC, United States.

[6] Division of Pediatric Hematology/Oncology, McMaster Children's Hospital, McMaster University, Hamilton, Ontario, Canada.

[7] Division of Clinical Pharmacology, Department of Pediatrics, Children's National Health System, Washington, District of Columbia, United States.

[8] Division of Paediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Basel, Switzerland

[9] Division of Neonatology, Department of Pediatrics, University of Calgary, Alberta Children's Hospital, Alberta, Canada.

[10] Division of Neonatology, Department of Pediatrics, McMaster Children's Hospital, McMaster University, Hamilton, Ontario, Canada.

Corresponding Author:
Katelyn Sushko, RN
McMaster University
1280 Main St West, L8S 4L8
Hamilton, ON, Canada
Email: sushkokj@mcmaster.ca

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Abstract

Background: Infants in the neonatal intensive care unit are at risk of peripheral tissue ischemia, which can result in limb necrosis. Off-label use of topical nitroglycerine (TNG) ointment has presented a viable treatment option for this condition. As of July 2018, production of TNG ointment has been discontinued in Canada. We aimed to systematically review the evidence on the use of TNG ointment and glyceryl trinitrate (GTN) patches in newborns with peripheral tissue ischemia and call for action on this drug shortage.

Methods: EMBASE, CINAHL, MEDLINE, PubMed, and Web of Science were searched from inception to April 2020 for articles that reported use of TNG ointment or GTN patch for treatment of peripheral tissue ischemia in newborns.

Results: We included 22 articles describing the use of TNG ointment or GTN patch in the treatment of 37 tissue ischemia events in 36 preterm and term neonates. Twenty-three infants received TNG ointment, 12 received GTN patch, and one received GTN patch and TNG ointment. Nineteen injuries treated with TNG ointment (83%) and seven treated with GTN patch (54%) showed complete recovery. Two infants treated with GTN patch experienced adverse events (methemoglobinemia) requiring early discontinuation of treatment.

Interpretation: TNG ointment presents a safe therapeutic option for salvage therapy of tissue ischemia in newborns. Its lack of availability can result in life-altering morbidities or use of unsuited alternatives with suboptimal efficacy and high risk of serious adverse events. The timely engagement of stakeholders is essential to address this important drug shortage in Canada.

Introduction

Extremely low birth weight (ELBW) infants in the Neonatal Intensive Care Unit (NICU), require venous with or without arterial cannulation to maintain their therapeutic needs. Although these interventions are "*non-negotiable,"* peripheral tissue ischemia is a well-described complication of vascular catheterization. Peripheral tissue ischemia is primarily attributed to iatrogenic causes, including extravasation of intravenously administered medication, peripheral vasospasm, or a thromboembolic event secondary to percutaneous arterial access.[1,2] Tissue injury mediated by arterial and venous catheterization presents significant morbidity among NICU graduates. The evidence on the incidence of any peripheral tissue ischemia among NICU survivors is variable but has been reported in up to 10% of ELBW infants, while up to 4% can suffer from severe tissue injuries or necrosis.[3,4,5,6]

The current approach to peripheral tissue ischemia in neonates is mainly limited to conservative treatment including removal of the device, elevation of the affected limb, and application of warmth to the opposite limb (reflex vasodilatation) with variable success.[1] Although antithrombotic and fibrinolytic agents as non-operative approach are promising therapeutic options in older children, their use in sick neonates of NICU is limited due to risk of serious bleeding.[7] Glyceryl trinitrate (GTN) patch and topical nitroglycerine (TNG) ointment with labelled indications of treatment of angina pectoris or pain associated with chronic anal fissure in adults have been used, off-label, as salvage therapy for tissue ischemia in neonates since the 1980s. In July 2018, the Canadian manufacturer discontinued the production of TNG ointment. We thus aimed to systematically review the available literature on the use of TNG ointment and GTN patch in newborn infants with peripheral tissue ischemia to address the potential impact of this drug shortage in Canada.

Methods

Reporting guidelines

This review was carried out as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] The protocol for this systematic review was not published.

Search strategy

The database EMBASE, CINAHL, MEDLINE, PubMed, and Web of Science were systematically searched from inception to April 2020. A search strategy for the electronic literature search in *Ovid Medline,* using the following key terms was performed: (intensive care units, neonatal/ OR intensive care, neonatal/ OR infant, newborn OR infant, premature/) AND (nitroglycerine/ OR glyceryl trinitrate.mp). This strategy was translated as appropriate for the other databases. We searched the bibliographies of any relevant articles for additional references. Using Google Scholar, we also searched for studies that are not commercially published, such as conference abstracts, dissertations, and policy documents. We did not apply any language or study design limitation. Animal studies and duplicate studies were excluded.

Study selection

All randomized controlled trials (RCTs), prospective and retrospective cohort studies, and case reports describing the use of TNG ointment or GTN patch in the treatment of tissue ischemia in hospitalized newborn infants of any gestational age and postnatal age were eligible for inclusion, irrespective of the dose, administration frequency and duration of treatment. Standard practice was the comparator in studies with a control group. If there was no comparator group, the reported efficacy and safety of TNG ointment or GTN patch during the observation period were extracted.

Data extraction

Following the database searches, two independent reviewers (KS and SSZ) screened the eligibility of the resulting articles at the title and abstract level and then at the full-text level. After identification of all studies to be included in the final review, the following data were extracted from each study using a standardized data collection form: first author, year of publication, study design, number of cases, infant gestational age, infant postnatal age, cause(s) of ischemia, ischemic site(s), the lag time between initiation of TNG ointment or GTN patch treatment and tissue injury, type of nitroglycerine preparation (ointment or patch), dose, time to the first effect defined as the time between the start of TNG ointment or GTN patch therapy and the first signs of improved perfusion recorded by the responsible care provider, treatment duration, adjunctive pharmacotherapy, primary outcome defined as complete recovery or no complete recovery, and adverse events.

Data quality assessment

We used the Critical Appraisal Checklist for Case Reports by the Joanna Briggs Institute (JBI)[9] to assess the risk of bias of individual studies, as all included studies, except for one retrospective audit, were case reports. Using the aforementioned tool, each study was evaluated to determine whether it provided a clear description of the following items: patient demographic characteristics, patient history, clinical condition, diagnostic tests and assessment methods along with their relevant findings, interventions or treatment procedures, post-intervention clinical condition, adverse or unanticipated events; and takeaway lessons. All studies were independently assessed by two reviewers (KS and SSZ). Any disagreements were resolved by discussion between three reviewers (KS, SSZ and CL).

Data analysis

As none of the included articles presented effect estimate statistics, a meta-analysis was not conducted. Instead, the results were summarized and presented narratively.

Ethics approval

We did not seek institutional ethics approval as our study did not constitute primary research and involved the access of publicly available evidence.

Results

A total of 741 articles were identified as a result of all database searches, a review of relevant reference lists, and a grey literature search (Figure 1). Following deduplication, 438 articles were screened at the title and abstract level and 23 were screened at the full-text level. Twenty-two studies[10-31] were included in the final review. All articles, except for one were case reports. The remaining article was an abstract of a retrospective audit. Extracted data are summarized in Table 1.

Characteristics of studies

Newborn infants and injuries

We identified 22 studies describing 36 neonates with 37 peripheral tissue ischemic events treated with TNG ointment (n = 23, 63.9%), GTN patches (n = 12, 33.3%), or both (n = 1, 2.8%) (Table 1). The majority of infants were extremely or very preterm (n = 24, 66%) and within the first two weeks of life at the time of injury (n = 25, 69%). Placement of an umbilical artery catheter or peripheral arterial line was the most common cause of identified tissue ischemia (n = 20, 54%), followed by intravenous drug administration (n = 5, 14%).

Treatment details

TNG ointment

Twenty-three infants received TNG ointment for 25 peripheral tissue ischemic events.[11,12,14-15,18-22,24,25,27,28,30,31] The time for initiation of treatment had a delay of up to 6 days. The time from application to first effect varied from 15 minutes after application to 23 days. Treatment duration ranged from one dose to 36 days with 19 (83%) injuries showing complete recovery.[11,12,14-15,20,22,24,25,27,30,31] Four adverse events were reported in infants treated with TNG ointment, three in the form of mild blood pressure and heart rate changes that resolved without discontinuation of treatment, and one occurrence of swelling bulla that resolved with the application of Xeroform gauze and limb elevation.[12,14,19] Six of the infants treated with TNG ointment received adjunctive therapy which included tissue plasminogen activator (tPA), heparin, intravenous nitroglycerine, 100% humidity, and milrinone.[19,22,24,27,28,30] One infant that experienced embolization of a broken arterial catheter tip was first treated by removing the catheter fragment using angiography.[22]

GTN patch

Twelve infants received GTN patches for 13 peripheral tissue ischemic events.[10,13,16,23,26,29] Time of application of GTN patch after tissue injury ranged from immediately to 12 hours after the injury. The maximum duration of treatment was seven days, with GTN discontinued in three peripheral tissue injuries due to serious adverse events.[29] Seven of the 13 injuries showed a completed recovery (54%).[10,13,16,23,26,29] Six of the ten infants treated with the GTN patch received adjunctive therapies which included enoxaparin, heparin, and tPA.[23,26]

Methemoglobinemia was the described adverse event subsequent to the use of the GTN patch in two infants.[29] In both cases, a 9 cm^2 patch (18.7 mg) was applied to the sites of peripheral tissue injuries. The first neonate received three GTN patches for two peripheral tissue

ischemic events (one spontaneous post-birth and one after a PAL insertion) over 48 hours. Two patches were applied on the first day of life and the third patch was applied on the second day of life. Within six hours following the application of the third patch, the infant's oxygen requirements increased from 0.21 to 0.40 and methemoglobin levels rose from 1.1% to 8.4%. In the second case, GTN patches were applied for peripheral tissue injury following a PAL insertion. One patch was applied on the third day of life and changed daily until the seventh day of life when two patches were applied and changed twice daily, with a total of ten patches used in five days. Within 24 hours of the application of two patches on the seventh day of life, the infant's oxygen requirements increased from 0.23 to 0.70 and methemoglobin levels increased to 23.3%. Symptoms of methemoglobinemia ceased within 24 hours of patch removal. One other infant experienced a mild decrease in blood pressure, which resolved with adjustment of inotropic support.[13]

GTN patch and TNG ointment

One infant was treated with both GTN patch and TNG ointment.[17] In this case, the patch was applied to the injury for five days as an alternative to TNG ointment as it was unavailable. Once the ointment was available, the patch was removed and ointment was applied for 11 days, along with an antibiotic cream. Following ointment application, rapid improvement was observed with increased vascularization and hyperemia of the ischemic tissue. No adverse events occurred throughout treatment with either the patch or ointment. Following treatment, partial loss of the distal phalange of one finger and one toe remained.

Risk of bias assessment

All studies met at least six of the eight criteria of the JBI appraisal tool. Fourteen of the included studies met all the eight criteria, with six missing only one criterion (Table 2).

Interpretation

In this systematic review, the efficacy of TNG ointment in newborn infants appears favorable, with 83% of tissue ischemic events treated with ointment experiencing complete recovery.[18,19,21,28] In the four cases where recovery was incomplete, extenuating circumstances might have mitigated the ointment's efficacy. In one case, the infant had reduced limb movement and reflexes with muscle atrophy at discharge as a result of Purple Glove Syndrome[28], a rare condition that has been known to progress to vascular compression and compartment syndrome requiring fasciotomy, skin grafting, or amputation in adults. The underlying pathology of Purple Glove Syndrome is poorly understood but it has been hypothesized to occur as a result of several mechanisms from tissue infiltration via extravasation of a highly alkaline substance (phenytoin) to venous obstruction following reaction of phenytoin with the more neutral pH of blood.[32] The application of TNG ointment may not be sufficient given this complex pathology. In the remaining cases, short duration of treatment or prolonged lag time in start of treatment might have contributed to insufficient recovery.[18,19,21]

Based on the available evidence, TNG ointment seems to be well tolerated in preterm and term neonates, with no significant adverse event reported with this therapy in this population. Reports of mild decrease in blood pressure were in infants already receiving inotropes for blood pressure support before TNG ointment application[12,14], which may suggest that TNG ointment was not the only factor contributing to hypotension. The results of our review point towards efficacy with minimal adverse events in the use of TNG ointment for treating neonatal peripheral tissue ischemia.

In contrast, there appeared to be a lack of efficacy as well as an occurrence of serious adverse events among the infants treated with GTN patches. In this review, almost half of the 13

tissue injuries treated with a GTN patch did not experience a complete recovery[10,13,23,26,29] and in two infants, serious adverse events of methemoglobinemia occurred, requiring treatment to be discontinued early.[29] While GTN patches may be more effective and/or safe in pediatric or adult populations[33,34], the available evidence does not support its use in neonates.

Limitations

To our knowledge, this is the first review to have summarized the entirety of the available literature on ointment and patch formulations of nitroglycerine products for salvage therapy in neonatal tissue ischemia. This allowed us to describe the neonatal outcomes across these therapies as well as to examine their safety. However, our review also has limitations. Due to the methodology of the available literature (primarily case reports), our review consisted of studies that are at the lowest level of medical evidence. As such, they are subject to vulnerabilities including a lack of ability to generalize, danger of over-interpretation, publication bias, and inability to establish a cause-effect relationship. To further the literature on this topic, future studies may use methods such as the cohort design.

Call to action for TNG in Canada

National drug shortage are known as a serious threat to patient safety and quality of care, especially for vulnerable patients of NICUs.[35] Indefinite discontinuation of TNG ointment in Canada is one clear example of how this important drug shortage may pose serious health risks. Although no randomized clinical trials are available, the available evidence on the use of TNG ointment in neonates with peripheral tissue ischemia has supported its efficacy with no reported serious adverse events. On the contrary, the limited available evidence on the use of GTN patches as an alternative pharmacotherapy has shown either a lack of efficacy or an occurrence of serious adverse events.

Peripheral tissue ischemia is a well-known and serious morbidity among ELBW infants. The low weight and high rate of comorbidities makes most available therapeutic options, in older children and adults, less viable in this population. Surgical or radiological thrombo-embolectomy is not considered an option for ELBW neonates.[37] The use of thrombolytic agents or anticoagulants is a challenge, considering the limited experience and high-risk of potential adverse events, especially in the first week of life.[38] Therefore, critically ill infants in the NICU with a limb-threatening acute event present a therapeutic challenge. To our knowledge, TNG ointment continues to be marketed in developed jurisdictions such as the United States and the United Kingdom, where, although off-label, it remains available for prevention of this potentially life-altering morbidity in their sick neonates. Discontinuation of TNG ointment in Canada due to its limited economic viability will single us out in this important drug shortage and can adversely affect the care of patients in Canadian NICUs.[39,40]

Conclusions

Although no clinical trials exist, the available literature support the efficacy and safety profile of TNG ointment as a salvage therapy of peripheral tissue ischemia in neonates. With the indefinite discontinuation of TNG ointment by the Canadian manufacture, critically ill infants have lost a valuable therapeutic option with no comparable alternative. We are calling for attention to the severity of the impact that the indefinite discontinuation of this drug might have on the care of ELBW infants in Canada and ask for timely engagement of stakeholders to address this important matter for this vulnerable population.

Conflict of interest

The authors received no financial support for the research, authorship, and/or publication of this article, and report no conflicts of interest.

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Fig. 1: PRISMA Flow Diagram

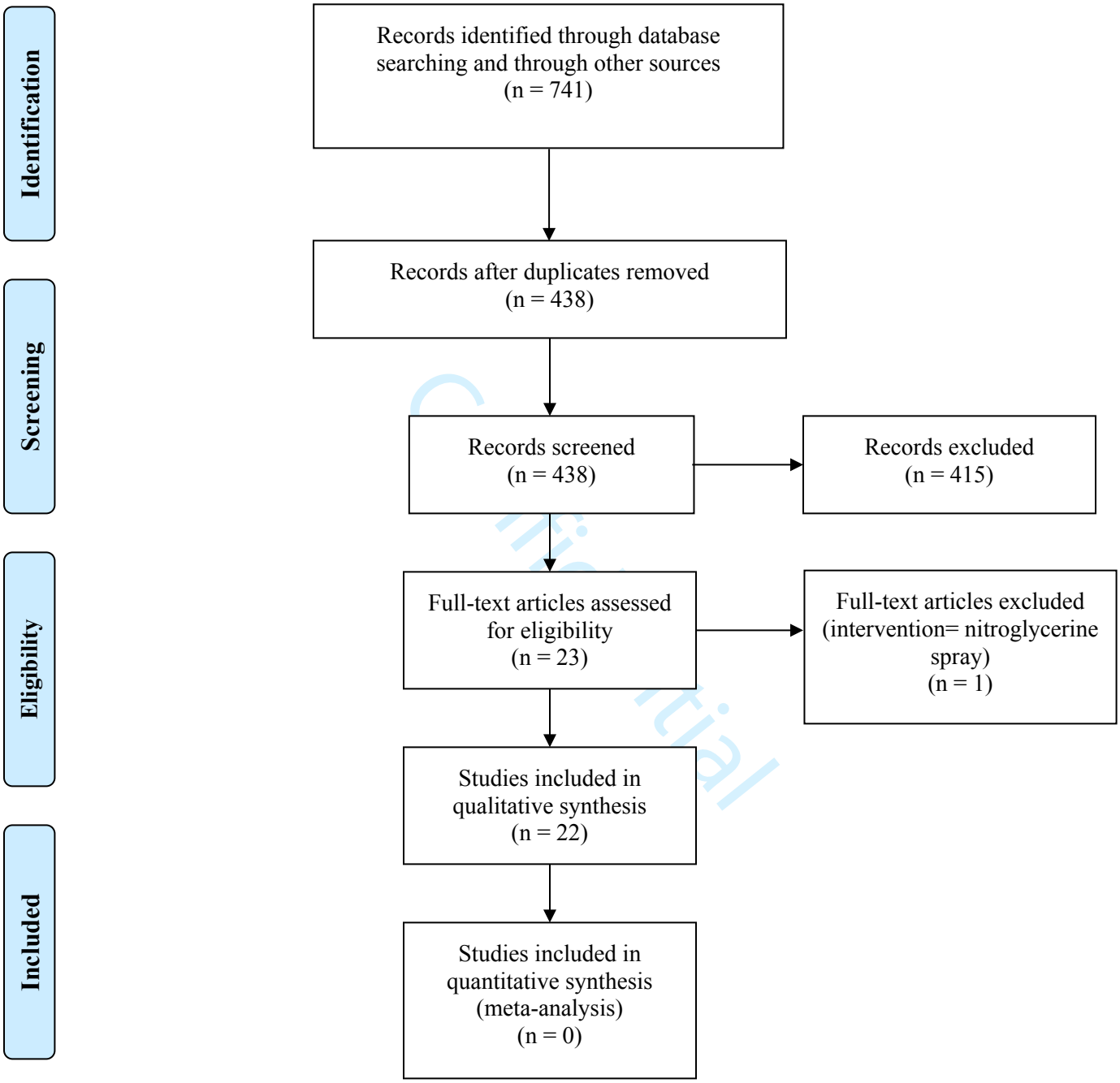

Table 1.
Use of topical nitroglycerine ointment and glyceryl trinitrate patch in neonatal peripheral tissue ischemia: Available evidence

First author (reference), year	No. of cases	GA, weeks	PNA, days	Cause of ischemia	Ischemic site	Time, h*	Dose	Time to first effect	Treatment duration	Outcome	Adverse events
Topical nitroglycerine ointment											
Denkler (11), 1989	1	34	1	Dopamine extravasation	Left hand to low forearm, left foot to knee	6	14 mm/kg†	Minutes	1 dose	CR	No
Wong (12), 1992	4	25 24 31 26	10 40 4 15	PAL PAL Dopamine extravasation Dopamine extravasation	Right hand Right hand Forearm, chest, axilla Forearm, arm	2 Within 24 1 0.5	4 mm/kg 4 mm/kg 4 mm/kg 4mm/kg	15 min 8 h 15 min 8 h	1 dose 12 h 1 dose 24 h	CR CR CR CR	No ↓BP No ↓BP, ↑HR
Baserga (14), 2002	3	30 25 23	1 1 10	UAC UAC PAL	Left leg, penis, scrotum Right leg Left hand	1 1.5 1	4 mm/kg 4 mm/kg 4 mm/kg	30 min 45 min 30 min	1 dose 1 dose 1 dose	CR CR CR	No No ↓BP
Vasquez (15), 2003	1	26	1	PAL	Left hand	7	<4 mm/kg	8 h	27 days	CR	No
Mousavi (18), 2010	1	32	2	UVC	Right leg and foot	NS	4 mm/kg	NR	NS	Death	No
Akingbola (19), 2012¶	1	31	60	PAL	Left leg, foot, and toes	Within 24	4 mm/kg	24 h	21 days	Loss of tip of left great toe	Swelling bulla
Mosalli (20), 2013	1	25	14	PAL	Right fingers	NS	< 4mm/kg	8 h	21	CR	No
Samiee-Zafarghandy (21), 2014	1	26	1.5	PIV	Left foot	144	4 mm/kg	24 h	14 days	Lost second and third toes	No
Dilli (22), 2015#	1	28	5	UAC	Lower limbs	NS	4 mm/kg	3 days	15	CR	No

Parra (24), 2016††	1	32	49	Thrombin injection into PSA sac	Right arm	NS	NS	NS	NS	CR	No
Vivar del Hoyo (25), 2016	4	24	NS	UAC/UVC	Toes	First hours after ischemia	4 mm/kg	NS	5-18	CR	No
		35		PICC	Fingers						
		>37		PICC	Fingers						
		>37		PICC	Fingers						
Han (27), 2017§§	1	24	5	PAL	Upper limb	48	4 mm/kg	23 days‡	36	CR	No
Isik (28), 2017¶¶	1	34	NS	PIV phenytoin infusion	Upper limb	NS	NS	Weeks	NS	Reduced movement/ reflexes, muscle atrophy	No
Kuttysankaran (30), 2018	1	Term	1	Spontaneous femoral artery thrombosis	Lower limb	NS	NS	2 days	4	CR	No
Weeraskera (31), 2019##	1	26	5	PIV	Fingers	NS	4 mm/kg	18 hours	14	CR	No
Glyceryl trinitrate patch											
O'Reilly (10), 1988	1	NS	NS	TPN extravasation	Dorsum of foot	2.5	0.2 mg	NS	1 h	CR	No
Varughese (13), 2001	1	33	10	UAC	Right hip	4	0.4 mg	7 h	30 h	CR	↓BP
Maffei (16), 2006	2	29	1	Central venous catheter	Left arm	0.5	1 cm^2 patch of Triniplas 5mg/7 cm^2	1 h	7 days	CR	No
		32	8	PAL	Right arm	1		3 h	4 days	CR	No
Teo (23), 2015**	1	32	NS	PICC	Upper limb	12 h after heparin initiation	NS	5 days	7	CR	No
Yong (26), 2016‡‡	5	<31	<14 - >28	PAL	NS	NS	NS	NS	NS	4 NR 1 CR	No
Mintoft (29), 2018	2	24	1	Spontaneous, PAL	Lower limbs, thumb,	Immediately	9 cm^2 patches containing	NS	2***	CR	Methemoglobinemia
		24	3, 7	PAL					5***	Loss of tips of toes	Methemoglobinemia

					forefinger Toes		18.7 mg GTN					
Topical nitroglycerine ointment and glyceryl trinitrate patch												
Ancora (17), 2006 *§*	1	28	1	UVC	Right fingers, right and left toes	At 8 h of life 120	NS	NS	5 11	Partial loss of distal phalange of finger and toe	No	

Start time after the tissue injury; †We calculated this dose by converting 1 inch of ointment (specified by Denkler) to mm and dividing by the infant's weight of 1.8 kg; ‡Improvement observed 23 days after admission to NICU; §Adjunctive therapy with antibiotic cream; ¶ tPA and heparin;# tPA, heparin, and intravenous nitroglycerine; **heparin and enoxaparin; ††heparin; ‡‡tPA and heparin; §§100% humidity; ¶¶heparin; ##heparin and milrinone; * Treatment discontinued due to methemoglobinemia; BP blood pressure; CR complete resolution; GA Gestational age; HR heart rate; NR no response; NS not stated; PAL peripheral arteria line; PICC peripherally inserted central catheter; PIV peripheral intravenous; PNA Postnatal age; PSA pseudoaneurysm; tPA tissue plasminogen activator; TPN total parenteral nutrition; UAC umbilical arterial catheter; UVC umbilical venous catheter; ↓ decrease; ↑ increase; < less than, > greater than*

Table 2.
Assessment of risk of bias of included studies

	Joanna Briggs Checklist Criteria							
Study	**Demographic characteristics**	**Patient history/ timeline**	**Clinical condition**	**Diagnostics/ assessments**	**Interventions/ treatments**	**Condition post-intervention**	**Adverse events**	**Takeaway lessons**
O'Reilly, 1988		+	+	+	+	+	+	+
Denkler, 1989	+	+	+	+	+	+	+	+
Wong, 1992	+	+	+	+	+	+	+	+
Varughese, 2001	+	+	+	+	+	+	+	+
Baserga, 2002	+	+	+	+	+	+	+	+
Vasquez, 2003	+	+	+	+	+	+	+	+
Maffei, 2006	+	+	+	+	+	+	+	+
Ancora, 2006	+	+	+	+		+	+	+
Mousavi, 2010	+	+	+	+		+	+	+
Akingbola, 2012	+	+	+	+	+	+	+	+
Mosalli, 2013	+	+	+	+	+	+	+	+
Samiee-Zafarghandy, 2014	+	+	+	+	+	+	+	+
Dilli, 2015	+	+	+	+	+	+	+	+
Teo, 2015	+	+	+	+		+	+	+
Parra, 2016	+	+	+	+		+	+	+
Vivar del Hoyo, 2016	+	+	+	+	+	+	+	+
Yong, 2016	+	+	+			+	+	+
Han, 2017	+	+	+	+	+	+	+	+
Isik, 2017	+	+	+	+		+	+	+
Mintoft, 2018	+	+	+	+	+	+	+	+
Kuttysankaran, 2018	+	+	+	+		+	+	+
Weeraskera, 2019	+	+	+	+	+	+	+	+

Contributor's statement for "Topical Nitroglycerin Ointment as Salvage Therapy for Peripheral Tissue Ischemia in Newborn Infants: A Systematic Review"

Please see below for how each of the authors of our manuscript has fulfilled the criteria for authorship of ICMJE:

	KS	CL	LF	AG	MMA	AKC	JVDA	TLM	SSZ
Contributed substantially to conception and design, or acquisition of data, or analysis and interpretation of data	x	x	x	x	x	x	x	x	x
Drafted the article or revised it critically for important intellectual content	x	x	x	x	x	x	x	x	x
Gave final approval of the version to be published	x	x	x	x	x	x	x	x	x
Agreed to act as guarantor of the work (ensuring that questions related to any part of the work are appropriately investigated and resolved).	x	x	x	x	x	x	x	x	x

Katelyn Sushko (KS), Catherine Litalien (CL), Lauren Ferruccio (LF), Andrea Gilpin (AG), Maryann Mazer-Amirshahi (MMA), Anthony K Chan (AKC), John van den Anker (JVDA), Thierry Lacaze-Masmonteil(TLM), Samira Samiee-Zafarghandy (SSZ)