Hospital Pharmacy

Phenytoin Induced Purple Glove Syndrome: An Effective Management Technique

Journal:	*Hospital Pharmacy*
Manuscript ID	HPX-23-0231
Manuscript Type:	Case Report
Date Submitted by the Author:	23-Oct-2023
Keywords:	Adverse Drug Reactions, Drug Interactions, Intravenous Therapy, Anticonvulsants

Complete List of Authors: Mutsago, Tonderai; Baits and The London NHS Trust, London Reconstructive Microsurgery Unit, Department of Plastic Surgery, Emergency Care and Trauma Division
Kazzazi, Danny; St Thomas' Hospital Ibrahim, Yahya; Barts and The London NHS Trust, London Reconstructive Microsurgery Unit, Department of Plastic Surgery, Emergency Care and Trauma Division Kazzazi, Fawz; Baits and The London NHS Trust, London Reconstructive Microsurgery Unit, Department of Plastic Surgery, Emergency Care and Trauma Division
Patel, Hasu; Baits and The London NHS Trust, London Reconstructive Microsurgery Unit, Department of Plastic Surgery, Emergency Care and Trauma Division
Pafitanis, Georgios; Baits and The London NHS Trust, London Reconstructive Microsurgery Unit, Department of Plastic Surgery, Emergency Care and Trauma Division

Abstract:

Background:
Purple glove syndrome (PGS) is a rare condition characterized by limb edema, discoloration, and pain associated with intravenous and oral phenytoin administration. The pathophysiology is poorly understood, and there is no established treatment. Simple cases have previously been managed with hyaluronidase subcutaneous injections, with more severe cases resulting in compartment syndrome, debridement, or even amputation.

Methods/Results:
In this case report, a 2-year-old boy with status epilepticus developed PGS after receiving intravenous phenytoin via a cannula on the dorsum of the right hand. The patient was successfully managed by locally infiltrating subcutaneous hyaluronidase diffusely to the affected area, titrating its dose to effect, rather than aiming to adhere to any specific dosing limitation. The child was reviewed daily by the Plastic Surgery team until being discharged, and focal lesions began to demarcate after 48 hours, with epidermal loss but no deeper trauma. The epidermis peeled within one month, with healthy ~~underlying~~ skin found underlying

	when followed up in clinic. Conclusions: This case illustrates that subcutaneous administration of hyaluronidase and titrating to effect provides an effective and safe treatment for treating distal cases of early PGS in children.

TITLE PAGE

Title: Phenytoin Induced Purple Glove Syndrome: An Effective Management Technique

Authors: Tonderai Mutsagul, Danny Kazzazi[2], Yahya Ibrahim', Fawz Kazzazi', Hasu Patel', Georgios Pafitanis'

Running title: Phenytoin Induced Purple Glove: Management with Hyaluronidase

Affiliation:

1. London Reconstructive Microsurgery Unit, Department of Plastic Surgery, Emergency Care and Trauma Division, The Royal London Hospital, Barts Health NHS Trust, London, UK
2. University College London, Gower St, London WC1E 6BT

Author of Correspondence: Mr Georgios Pafitanis, georgios.pafitanis@nhs.net

Author Contributions: all authors contributed to the writing, design, editing, and submission of the manuscript.

Keywords: purple glove syndrome, phenytoin, hyaluronidase

Funding: there was no funding for this study.

Disclosure of competing interests: no authors have any disclosures of competing interests.

Ethical Statement: written consent has been obtained from the parents of the patient.

Tables: 0

Figures: 11

Videos: 0

Abstract

Background:

Purple glove syndrome (PGS) is a rare condition characterized by limb edema, discoloration, and pain associated with intravenous and oral phenytoin administration. The pathophysiology is poorly understood, and there is no established treatment. Simple cases have previously been managed with hyaluronidase subcutaneous injections, with more severe cases resulting in compartment syndrome, debridement, or even amputation.

Methods/Results:

In this case report, a 2-year-old boy with status epilepticus developed PGS after receiving intravenous phenytoin via a cannula on the dorsum of the right hand. The patient was successfully managed by locally infiltrating subcutaneous hyaluronidase diffusely to the affected area, titrating its dose to effect, rather than aiming to adhere to any specific dosing limitation. The child was reviewed daily by the Plastic Surgery team until being discharged, and focal lesions began to demarcate after 48 hours, with epidermal loss but no deeper trauma. The epidermis peeled within one month, with healthy underlying skin found underlying when followed up in clinic.

Conclusions:

This case illustrates that subcutaneous administration of hyaluronidase and titrating to effect provides an effective and safe treatment for treating distal cases of early PGS in children.

Introduction

Purple glove syndrome (PGS) is a rare condition characterized by limb edema, discoloration, and pain associated with intravenous and oral phenytoin administration. (The incidence following intravenous administration ranges from 1.7% to 5.9%) The pathophysiology is poorly understood, but histopathologic studies have demonstrated that it occurs in three stages.[2] In the first 2-12 hours after infusion, a blue-purple discolouration appears at the site of cannulation; in the following 12 hours, this spreads distally and is accompanied by oedema — with or without blistering. In the final stage, there is typically a resolution of signs within days to weeks, but it can progress to compartment syndrome, ischaemia, and necrosis.[3] Some authors have speculated as to the pathophysiology of the condition is related to the administration — either due to poor technique or co-infiltration with other substances (the weak acids that stabilize it such as sodium hydroxide, propylene glycol and ethanol).[45] Meanwhile, other authors have favoured biochemical explanations for its occurrence, such as: its alkalinity stimulating vasoconstriction, thrombosis, and subsequent leakage/oedema due to endothelial damage;[6] or the protein-binding of the drug intravascularly increasing the oncotic pressure.?

Commented [RL1]: Maybe the authors could address the differentiation of this syndrome from what is caused if the IV phenytoin is inadvertently infused into a distal artery

Ultimately, the pathophysiology remains unknown, but its risk factors are fast infusion rates, older patients, small gauge cannulas, multiple infusions, and large doses.[4] The possible sequelae can range from mild oedema to severe cases resulting in compartment syndrome, debridement, amputation, or even death.[89] Despite this, there is no established treatment. Mild cases in the literature have been managed with simple elevation and warm/cold compresses;[1°] ulcers have been managed with saline cleaning and dressing changes;[6] while various other proposals have been made for treatment of severe cases including systemic anti-coagulation, topical nitroglycerin, or local infiltration of one of many substances including hyaluronidase, hydrocortisone, triamcinolone, or heparin.[8] Many studies have also proposed the use of regional nerve blockade with mixed outcomes of skin or sensory deficits.[8] Where hyaluronidase has

been used previously, a low fixed rate dose (24 units) has been utilized in infants (14-month old male).[11] There is no consensus on the appropriate dose of hyaluronidase in paediatric patients.

Methods & Results

A ~~2 year-old~~2-year-old boy (weighing 20kg) was admitted with status epilepticus on a background of neonatal encephalopathy and epilepsy. He was already intubated and on the paediatric intensive care unit (PICU) at the time of referral to plastic surgery for purple discolouration to the digits of the right hand (figures 1 & 2).

The patient was given his first dose of IV phenytoin via a cannula on the dorsum of the right hand (loading dose of 20mg/kg). Purple discolouration was noted by the nursing staff and eventually a referral to plastic surgery was made 5 hours after the dose was given. The purple lesions involved the tips of the index and middle fingers within 2 minutes before spreading to the radial aspect of the index finger and the middle finger over the next hour. The hand was kept elevated and warm with the use of clinical gloves filled with warm water and blankets. 2% glycerol trinitrate ointment was applied. At this point, the provisional diagnosis by the intensive care team was discolouration secondary to hypovolaemia or thrombosis/micro-emboli; the patient was not on any inotropic or vasopressor medicines.

Five hours following the infusion, the fingertips were non-blanching and firm on palpation and the hand was mildly swollen. Importantly, palpation of the purple area appeared to be painful — with the child retracting to pain despite being intubated. The PICU staff had kept the cannula in situ.

Following a plastic surgery review, this was recognized as an isolated injury affecting a single limb that appeared following administration of IV phenytoin. A provisional diagnosis of PGS was made after consulting product/drug literature. A decision was made to treat with hyaluronidase as it was the reagent that practitioners were most

familiar with, and it was easily accessible. It was preferred to local anaesthetic & regional block techniques, considering the diagnosis of status epilepticus and a concern that further local anaesthetic may be clinically detrimental. Hyaluronidase was prepared with 1500 IU, dissolved into lml of 0.9% normal saline. The hyaluronidase saline solution was injected with an insulin needle into the subcutaneous tissue of the affected area. A total of 0.5m1 was injected (750 1-11)??. Initially 0.4m1 over 15 minutes. The discolouration was seen to recede within 5-10 minutes (figures 3 & 4). A further 0.1m1 was given 2 hours later and improvements seen at 6 hours post-infiltration (figures 57). No further phenytoin was given and W access was sought elsewhere, with the culprit cannula removed.

The child was reviewed daily by the Plastic Surgery team until being discharged. Focal lesions began to demarcate after 36 hours and were confined only to the pulps of both fingers (figures 8 & 9), with epidermal loss but no deeper trauma. These focal areas were found to bleed when pricked with a needle at the time and 4 days after injury (figures 10 & 11), with no sign of necrosis. The epidermis peeled within 1 month, with healthy underlying skin found underlying when followed up in clinic.

Discussion

This case study adds to the literature that supports the use of hyaluronidase in the treatment of PGS. In this case, it was used successfully within 6 hours in the early phase of the disease before proximal progression had occurred. This is the first publication to advocate for titrating the dose of hyaluronidase to effect in paediatric patients — with a safe outcome achieved with a dose of 750 IU.

This is the first case report to demonstrate the effective subcutaneous intralesional infiltration of a hyaluronidase dose titrated to response in PGS in paediatric patients. It shows a safe and effective resolution of signs with a dose of 750 IU with the patient followed-up in the outpatient setting following discharge. It adds to the limited literature on the subject. The drawbacks are that it is a single case report (level IV

evidence) with no case-control and where the exact mechanism of action is unknown.

There is no current consensus on the management of extravasations with hyaluronidase in paediatric patients with literature demonstrating a range from 15 units to 1500 units.[12] In a standard extravasation, the standard dose is 15 units in paediatric patients and 150 units in adults.[13] However, in the treatment of severe extravasation injury (classed as grade 3 or 4 [i.e. with evidence of epidermolysis or necrosis[14]]), then a paediatric dose of 150 units is recommended for vesicant chemotherapeutics.[15] A recent survey of paediatric intensive care units in the NHS found that teams would like to see more information on the use of hyaluronidase as a tool in the management of their patients — particularly in extravasation injuries.[16] The last published case report on the use of hyaluronidase in an infant (14 month old) with PGS was over 25 years ago; in that study, a fixed-rate dose of 24 units was used.[11] In this case we have successfully managed the patient by locally infiltrating subcutaneous hyaluronidase diffusely to the affected area, and titrating its dose to effect, rather than aiming to adhere to any specific dosing limitation. The total dose administered was 750 IU (0.5m1 of a standard 1500 IU/ml solution).

The exact mechanism by which PGS occurs is unknown, with several theories proposed — as previously discussed. Hyaluronidase is an endoglycosidase and breaks down hyaluronic acid into monosaccharides; hyaluronic acid is a major component of the extracellular matrix (ECM) and is found in multiple organs (testis, spleen, skin, eyes, liver, kidneys) as well as in body fluids (tears, blood, semen).[17] Its utility in drug-induced injuries (e.g. extravasation) is thought to be as this depolymerization of the ECM increases tissue permeability to aid in dispersion of the infiltrated agents.[13] Accordingly, it can only be assumed here a similar mechanism for dissolution was employed when the hyaluronidase was injected.

The implications here are twofold. First, this case report further supports the use of hyaluronidase in PGS. Secondly, that a dose can be selected dependent on the response

to the agent and — in our case — safely at 750 IU. Further study of this condition and its potential treatments is required. This includes developing a better understanding of the mechanism of PGS, the action of hyaluronidase, and the best management of PGS.

Conclusions

This case and importantly titrating to effect, with no fixed dose (up to the maximum safe reported limits for the paediatric population), provides an effective and safe treatment for treating distal cases of early cases of PGS in children. In more proximal cases, clinician discretion regarding dosage and the practicalities of subcutaneous injections should be considered.

Acknowledgements

No funding sources.

A special thank you to Ms. Hasu Patel who helped greatly in preparing this manuscript but passed away — we are grateful to her expertise, knowledge, and guidance.

References

1. Bumeo JG, Anandan J V., Barkley GL. A prospective study of the incidence of the purple glove syndrome. *Epilepsia.* 2001;42(9):1156-1159. doi:10.1046/J.1528-1157.2001.12901.X
2. Bhattacharjee P, Glusac EJ. Early histopathologic changes in purple glove syndrome. *J Cutan Pathol.* 2004;31 (7): 513-515. doi: 10.1111/J.0303 -6987.2004.00224.X
3. Pare JR, Moore CL. Intravenous Infiltration Resulting in Compartment Syndrome: A Systematic Review. *J Patient Saf* 2018;14(2):e6-e8. doi:10.1097/PTS.0000000000000233
4. O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology.* 1998;51(4):1034-1039. doi:10.1212/WNL.51.4.1034
5. Lalla R, Malhotra HS, Garg RK, Sahu R. Unexpected outcome (positive or negative) including adverse drug reactions: Purple glove syndrome: a dreadful complication of intravenous phenytoin administration. *BMJ Case Rep.* 2012;2012. doi:10.1136/BCR-2012-006653
6. Rajabally H, Nageshwaran S, Russell S. An atypical case of Purple Glove syndrome: an avoidable adverse event. *Case Reports.* 2012 ;2012 :b cr0120125653. doi:10.1136/BCR.01.2012.5653
7. Chokshi R, Openshaw J, Mehta NN, Mohler E. Purple glove syndrome following intravenous phenytoin administration. *Vascular Medicine.* 2007; 12(1): 29-31. doi:10.1177/1358863X07076551
8. Garbovsky LA, Drumheller BC, Perrone J. Purple Glove Syndrome after Phenytoin or Fosphenytoin Administration: Review of Reported Cases and Recommendations for Prevention. *Journal of Medical Toxicology.* 2015;11(4):445. doi:10.1007/S13181-015-0490-Z
9. Tsang CY, Ng JY, Yuen SH, Leung YF, Frcsed F, Surgery O. Purple glove syndrome caused by intravenous phenytoin: two case reports. *Hong Kong Medical Journal.* 2019;25(6):487489. doi:10.12809/hIcmj 176974
10. Nogal GP Del, Rodaniche A, Saragadam SD, Nogal GP Del, Rodaniche A, Saragadam SD. Purple Glove Syndrome: Recognizing a Rare Complication of Intravenous Phenytoin. *Cureus.* 2022;14(4). doi: 10.7759/CUREUS .23958
11. Sokol DK, Dahlmann A, Dunn DW. Hyaluronidase treatment for intravenous phenytoin extravasation. *J Child Neurol.* 1998;13(5):246-247. doi:10.1177/088307389801300512
12. Yan YM, Fan QL, Li AQ, Chen JL, Dong FF, Gong M. Treatment of Cutaneous Injuries of Neonates Induced by Drug Extravasation with Hyaluronidase and Hirudoid. *Iran JPediatr.* 2014;24(4):352. Accessed March 15, 2023. /pmc/articles/PMC4339556/
13. Maly C, Fan KL, Rogers GF, et al. A primer on the acute management of intravenous extravasation injuries for the plastic surgeon. *Plast Reconstr Surg Glob Open.* 2018;6(4). doi:10.1097/GOX.0000000000001743
14. Heckler FR. Current Thoughts on Extravasation Injuries. *Clin Plast Surg.* 1989;16(3):557563. doi:10.1016/S0094-1298(20)31322-5
15. Schulmeister L. Vesicant chemotherapy extravasation antidotes and treatments. *Clin J Oncol Nurs.* 2009;13(4):395-398. doi:10.1188/09.CJON.395-398
16. Corbett M, Marshall D, Harden M, Oddie S, Phillips R, McGuire W. Treating extravasation

injuries in infants and young children: a scoping review and survey of UK NHS practice. *BMCPediatr*. 2019;19(1). doi:10.1186/S12887-018-1387-1

17. Jung H. Hyaluronidase: An overview of its properties, applications, and side *effects*. *Arch Plast Surg*. 2020;47(4):297. doi:10.5999/APS.2020.00752

Figure Legends

Figure 1: Affected right hand with cannula in situ at referral.

Figure 2: Anterior-posterior view of purple discolouration to the right index finger and right middle finger at referral.

Figure 3: 2 minutes following treatment administration with receding of the purple discolouration (lateral view).

Figure 4: 2 minutes following treatment administration with improvement in the purple discolouration (anterior-posterior view).

Figure 5: 6 hours following treatment administration with improvement in the purple discolouration (anterior-posterior view).

Figure 6: 6 hours following treatment administration with receding of the purple discolouration (lateral view).

Figure 7: 6 hours following treatment administration with receding of the purple discolouration (oblique view).

Figure 8: 36 hours following treatment administration with improvement in the purple discolouration (posterior-anterior view).

Figure 9: 36 hours following treatment administration with improvement in the purple discolouration and small areas of epidermolysis (lateral view).

Figure 10: 4 days following treatment administration with significant improvement in the purple discolouration and pin-prick test demonstrating bleeding (lateral view).

Figure 11: 4 days following treatment administration with significant improvement in the purple discolouration and pin-prick test demonstrating bleeding (anterior-posterior view).

Figure 1: Affected right hand with cannula in situ at referral.

423x564mm (72 x 72 DPI)

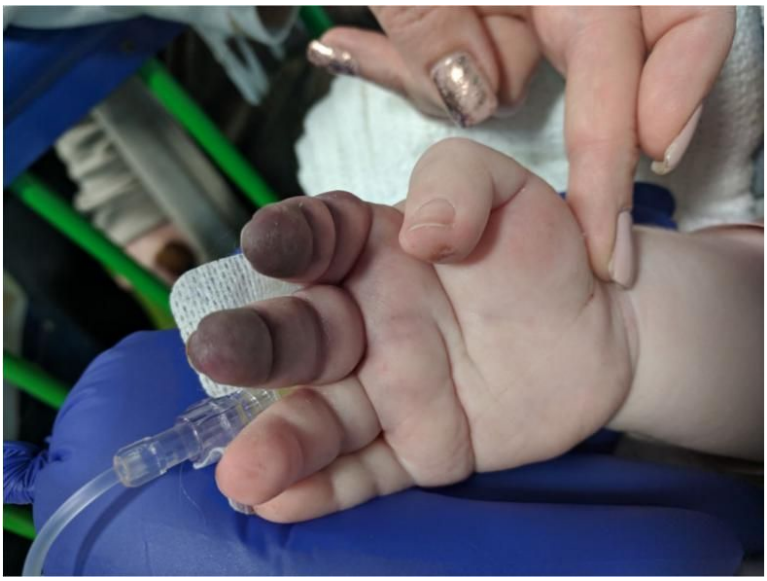

Figure 2: Anterior-posterior view of purple discolouration to the right index finger and right middle finger at referral.

564x423mm (72 x 72 DPI)

Figure 3: 2 minutes following treatment administration with receding of the purple discolouration (lateral view).

1422x1066mm (72 x 72 DPI)

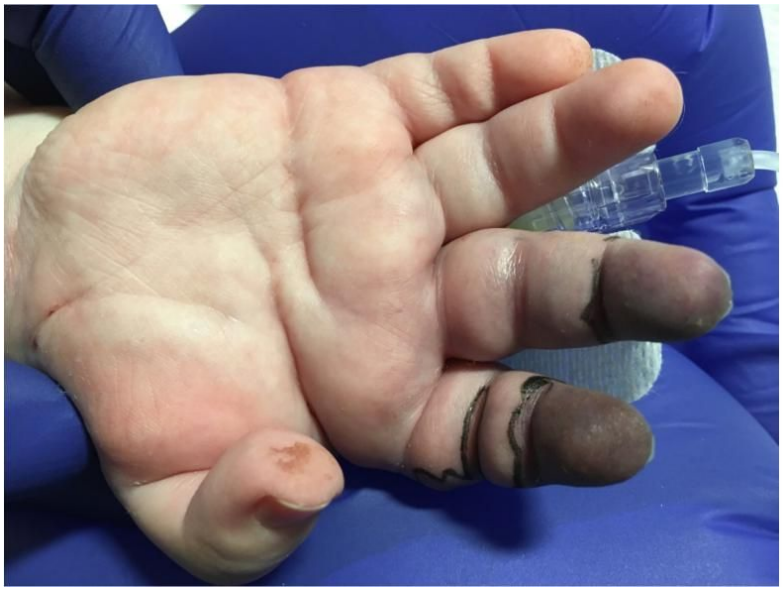

Figure 4: 2 minutes following treatment administration with improvement in the purple discolouration (anterior-posterior view).

1422x1066mm (72 x 72 DPI)

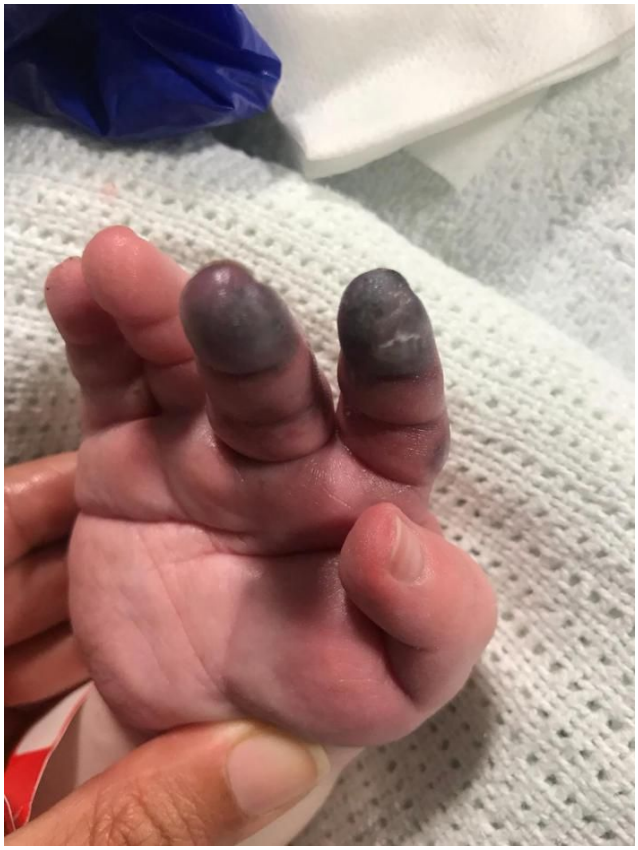

Figure 5: 6 hours following treatment administration with improvement in the purple discolouration (anterior-posterior view).

423x564mm (72 x 72 DPI)

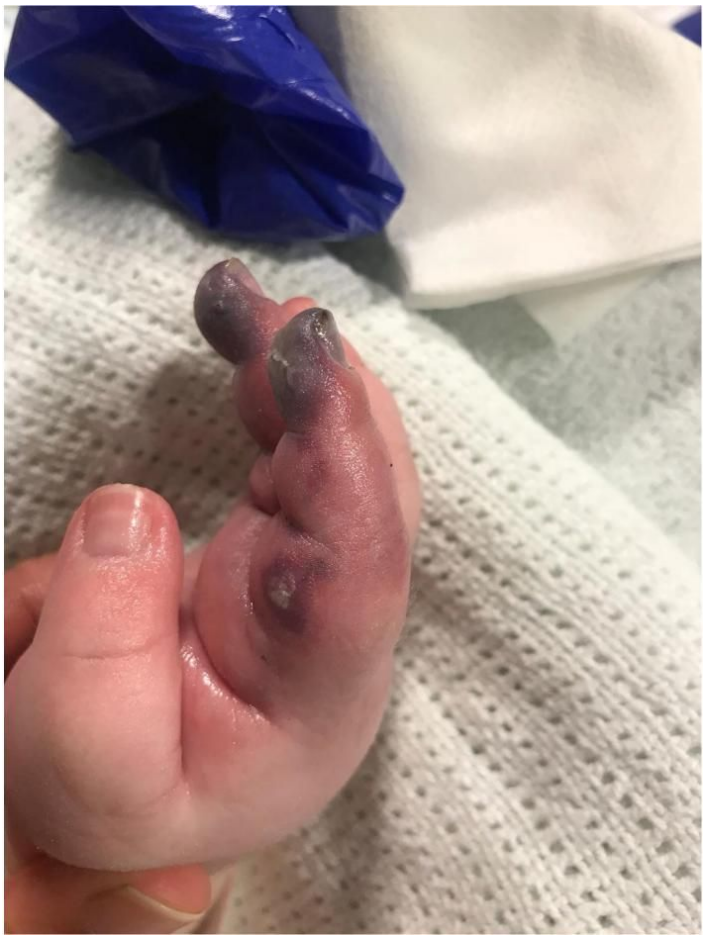

Figure 6: 6 hours following treatment administration with receding of the purple discolouration (lateral view).

423x564mm (72 x 72 DPI)

Figure 7: 6 hours following treatment administration with receding of the purple discolouration (oblique view).

423x564mm (72 x 72 DPI)

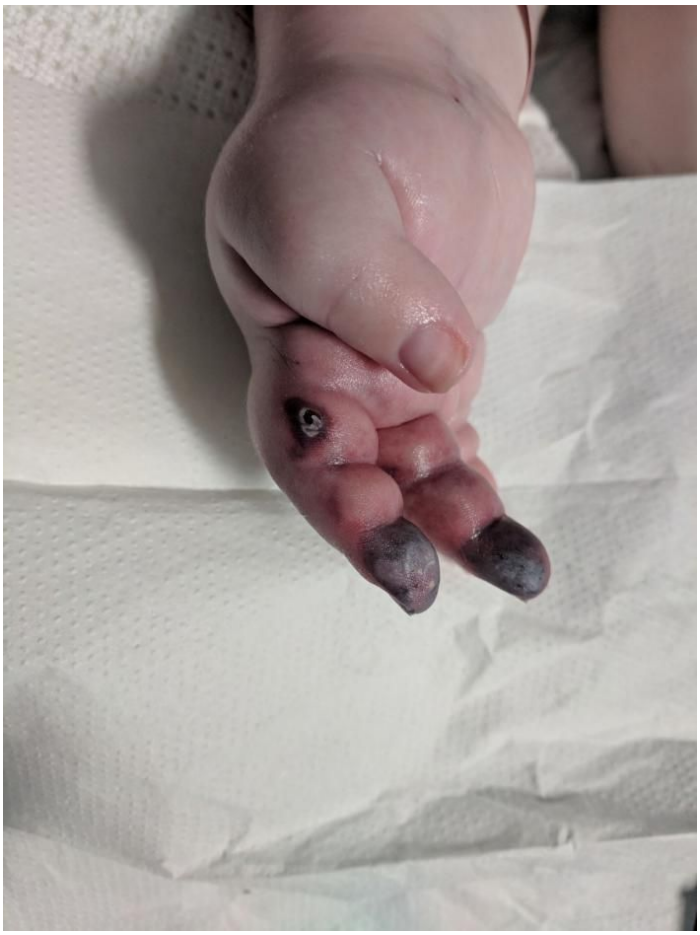

Figure 9: 36 hours following treatment administration with improvement in the purple discolouration and small areas of epidermolysis (lateral view).

423x564mm (72 x 72 DPI)

Figure 10: 4 days following treatment administration with significant improvement in the purple discolouration and pin-prick test demonstrating bleeding (lateral view).

1422x1066mm (72 x 72 DPI)

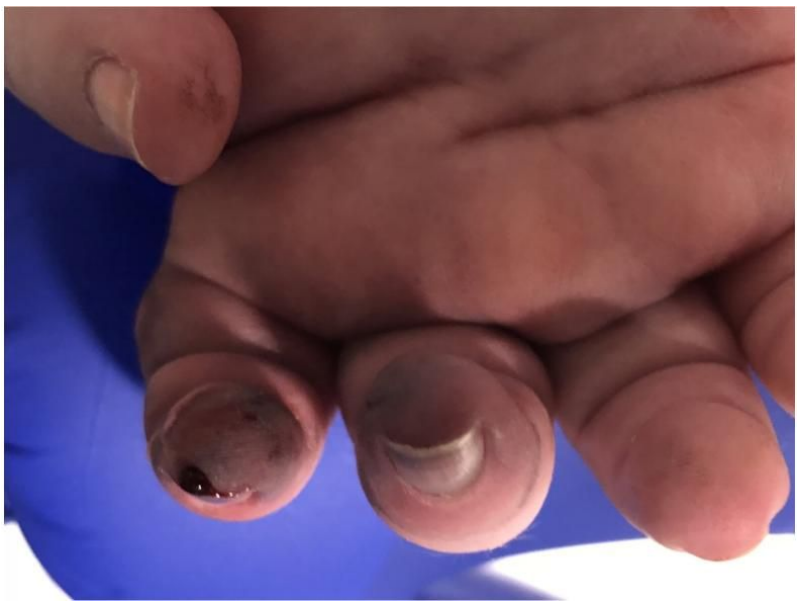

Figure 11: 4 days following treatment administration with significant improvement in the purple discolouration and pin-prick test demonstrating bleeding (anterior-posterior view).

1422x1066mm (72 x 72 DPI)