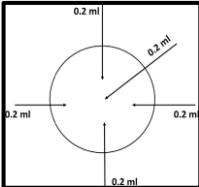


Hyaluronidase

Newborn use only


2022

Alert	Subcutaneous route only. Not for intravenous use. International units (IU) are hereafter referred to as “units”. For vasopressor induced ischaemic injuries, topical glyceryl trinitrate is preferred (Refer to ANMF glyceryl trinitrate formulary)										
Indication	Stage III-IV extravasation injury ⁽¹⁻⁴⁾ <table border="1"> <thead> <tr> <th>Stage</th> <th>Characteristics</th> </tr> </thead> <tbody> <tr> <td>I</td> <td>Painful intravenous (IV) site, no erythema, no swelling</td> </tr> <tr> <td>II</td> <td>Painful IV site, slight swelling, no blanching, good pulse below IV site, brisk capillary refill below IV site</td> </tr> <tr> <td>III</td> <td>Painful IV site, marked swelling, blanching, skin cool to touch, good pulse below IV site, brisk capillary refill below IV site</td> </tr> <tr> <td>IV</td> <td>Painful IV site, very marked swelling, blanching, skin cool to touch, decreased or absent pulse, capillary refill of more than 4 seconds, skin breakdown or necrosis</td> </tr> </tbody> </table>	Stage	Characteristics	I	Painful intravenous (IV) site, no erythema, no swelling	II	Painful IV site, slight swelling, no blanching, good pulse below IV site, brisk capillary refill below IV site	III	Painful IV site, marked swelling, blanching, skin cool to touch, good pulse below IV site, brisk capillary refill below IV site	IV	Painful IV site, very marked swelling, blanching, skin cool to touch, decreased or absent pulse, capillary refill of more than 4 seconds, skin breakdown or necrosis
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Action	Degrades hyaluronic acid in tissues and promotes rapid dispersal and absorption of extravasated medications										
Drug type	Enzyme										
Trade name	Hyalase										
Presentation	1500 international units (IU) powder for injection ampoule.										
Dose	Dose is dependent on the extravasated medication, stage and extent of extravasation, and size of the infant. Subcutaneous injection (hyaluronidase only) For Non-chemotherapeutic agents⁽⁵⁻⁷⁾ 150 - 200 units* *For smaller and lower grade injuries, doses as low as 15 units may be sufficient. For Chemotherapeutic agents⁽⁸⁾ 150 - 900 units Saline irrigation (hyaluronidase with sodium chloride 0.9%)^(5,7,9) 500 - 1500 units										
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – Not applicable. Renal impairment – Not applicable. Hepatic impairment - Not applicable.										
Maximum dose											
Total cumulative dose											
Route	Subcutaneous										
Preparation	Add 1 mL of water for injection or sodium chloride 0.9% to powder to make a 1500 units/mL solution. FURTHER DILUTE 0.1 mL (150 units) with 0.9 mL sodium chloride 0.9% to make a final volume of 1 mL with a final concentration of 150 units/mL. The solution should be used immediately after preparation. ⁽¹⁴⁾										
Administration	Ideally administer within 1-3 hours of extravasation but may still be helpful up to 72 hours after extravasation. ⁽⁵⁾ Subcutaneous injection (hyaluronidase only)⁽¹⁰⁾ Inject 0.2 mL aliquots subcutaneously into 5 sites (total 1 mL) using insulin syringe needle (gauge 28-31) around the perimeter of the extravasation. The procedure can be repeated if required. ⁽¹⁰⁾ <div style="text-align: center;">  </div>										

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	<p>Saline irrigation (hyaluronidase with sodium chloride 0.9%) ⁽⁹⁾</p> <p>Step 1: Clean the affected and surrounding area using aseptic techniques.</p> <p>Step 2: Infiltrate with 1% lignocaine for local anaesthesia.</p> <p>Step 3: Inject hyaluronidase, 500 - 1500 units, into the subcutaneous tissue beneath the damaged skin.</p> <p>Step 4: Make 4 small punctures in the tissue plane with a scalpel blade around the area to be treated.</p> <p>Step 5: Insert blunt needle (e.g. drawing up needle) subcutaneously through one of the puncture sites.</p> <p>Step 6: Using a syringe attached to a three way tap, inject sodium chloride 0.9%; this should flow freely out from the other three incisions.</p> <p>Step 7: Repeat the process, injecting through each incision and using in total up to 500 ml of sodium chloride 0.9%.</p> <p>Step 8: If during the procedure the limb becomes oedematous, perform a gentle massage towards the incision site to remove the excess fluid.</p> <p>Step 9: Dress the damaged area and keep covered for 24 to 48 hours.</p>
	
Monitoring	Continuous cardiorespiratory monitoring during the procedure
Contraindications	Hypersensitivity to hyaluronidase. Area of infection or acute inflammation near the injection site due to an increased risk of spreading a localised infection.
Precautions	
Drug interactions	
Adverse reactions	Local irritation, bruising and bleeding. Allergic reactions such as urticaria, angioedema, erythema and anaphylactic-like reactions. Overdose may lead to tachycardia, hypotension, vomiting and dizziness.
Compatibility	Water for injection, sodium chloride 0.9%, sodium chloride 0.45%, glucose 5%, glucose 10%
Incompatibility	Furosemide, benzodiazepines, phenytoin, heparin and adrenaline (epinephrine).
Stability	Discard any unused drug
Storage	Store below 25°C
Excipients	Sodium hydroxide
Special comments	Hyaluronidase injection is preferred for extravasation of irritants and vesicant medications. For extravasation of vasopressors, the vasodilator effect of topical glyceryl trinitrate may be desirable.
Evidence	<p>Efficacy</p> <p>Research studies reporting efficacy of hyaluronidase in neonates are limited to case reports and small cohort studies. In a survey of clinical practice, 38% neonatal units in Australia and New Zealand reported use of hyaluronidase for the management of neonatal extravasation injury.⁽¹⁾</p> <p>Sagheb et.al, retrospectively reviewed 20 neonates of mean gestational age of 32 weeks who had stage 3 and 4 extravasation injuries. Neonates with stage 1 -2 injuries and those caused by dopamine or alpha agonists were excluded. All grade 3 and 4 extravasation wounds (n=16) received hyaluronidase subcutaneously. An insulin syringe needle with a gauge range of 28–31 was used for injections of 0.2 mL of the solution (150 IU/mL) into 5 points of the wound circle. The procedure was repeated every 5 min at different points in a smaller circle to the core. They also used normal saline irrigation, fibrinolysin ointment and phenytoin ointment for wound care. In their study, none of the wounds developed any complications and surgical management was not required. All the lesions healed completely and the patients were discharged without sequelae.⁽¹⁰⁾</p> <p>Casanova et. al., reported 14 neonates with extravasation injuries caused by dopamine (n=9), caffeine (n=2), calcium (n=2) and beta blocker (n=1). The extravasation site was rinsed initially and followed by hyaluronidase injection through four peripheral micro incisions until the skin was properly taut. Finally,</p>

	<p>aspiration with a 2 mm microcannula and a 20 mm syringe was carried out. This procedure was repeated several times, rinsing the area with saline after each infiltration of hyaluronidase. Authors reported good results in 11 neonates however 3 neonates progressed to skin necrosis. In two of the three failures, the skin was severely damaged, either due to a highly toxic product (beta blocker) or to the delay before the procedure was implemented as hyaluronidase was used > 12 hours after extravasation.⁽³⁾</p> <p>Hyaluronidase might be efficacious in extravasation injuries by chemotherapeutic agents. In a small cohort of 7 patients with malignancy, 150-900 units of hyaluronidase was used for treatment after the accidental extravasations of Vinca alkaloids. No patient developed subsequent skin necrosis.^(8,11)</p> <p>Saline irrigation: To date, no randomised controlled trials have examined the effects of saline irrigation with or without prior hyaluronidase infiltration on the management of extravasation injury in neonates. Frequent reports in the literature indicate that saline irrigation is used for the management of extravasation injury in neonates.⁽¹³⁾ Davis et. al., infiltrated an area of mottled and discoloured skin at the IV infusion site in two extremely preterm infants with hyaluronidase 500-1000 units and 500 mL 0.9% sodium chloride irrigation. Four small punctures were made in the tissue plane with a scalpel blade around the area following local anaesthesia. A blunt cannula was then inserted subcutaneously through one of the puncture sites. Using a syringe, saline was injected to ensure free flow out from the other three incisions. The process was repeated, injecting through each incision. On review at 48 hours, the tissue looked healthy, well perfused and subsequently healed with minimal scarring.⁽⁹⁾</p> <p>Optimum time for treatment</p> <p>Hyaluronidase appears to be more efficient when it is used early. Casanova reported better outcomes when the treatment was performed within 6 hours of extravasation. In their study, the outcome was also dependent on the type of toxic agent and the extent of skin damage.⁽³⁾</p> <p>In a series of 12 cases Yan et. al., found good outcomes when hyaluronidase was administered up to 7-14 hours after extravasation. In 11 infants, hyaluronidase was given within 7 hours after extravasation and in 1 infant, 14 hours after extravasation. There was symptomatic improvement in all of them and follow up of 9 infants at 2 months showed negligible loss of function in the involved areas.⁽⁵⁾</p> <p>Safety</p> <p>There is scarcity of studies reporting safety of hyaluronidase subcutaneous injection in neonates.</p> <p>Pharmacokinetics</p> <p>Knowledge of the mechanisms involved in the disappearance of injected hyaluronidase is limited. The reconstitution of the dermal barrier removed by the intradermal injection of hyaluronidase is inversely related to the dose but the barrier is completely restored in all treated areas at 48 hours.</p>
<p>Practice points</p>	<ul style="list-style-type: none"> • Stages 1 and 2 extravasations are managed conservatively by cessation of infusion, reflex vasodilation, dressings, elastic bandaging and limb elevation. • Input from wound management team will be helpful. • Topical glyceryl trinitrate ointment may be effective for ischaemic tissue injuries. • For vesicant fluid extravasation injuries, prompt administration of antidote and surgical management may be required. • For smaller and lower grade injuries, doses as low as 15 units may be sufficient.
<p>References</p>	<ol style="list-style-type: none"> 1. Restieaux M, Maw A, Broadbent R, Jackson P, Barker D, Wheeler B. Neonatal extravasation injury: prevention and management in Australia and New Zealand—a survey of current practice. <i>BMC Pediatr.</i> 2013 Mar 11;13:34. 2. Cho K, Ahn H, Lee J. Extravasation Wound Care in the Neonatal Intensive Care Unit. <i>J Wound Manag Res</i> 2019 March;15(1):17-22. 3. Casanova D, Bardot J, Magalon G. Emergency treatment of accidental infusion leakage in the newborn: report of 14 cases. <i>Br J Plast Surg.</i> 2001 Jul;54(5):396-9. 4. Ong J, Van Gerpen R. Recommendations for Management of Noncytotoxic Vesicant Extravasations. <i>J Infus Nurs.</i> 2020 Nov/Dec;43(6):319-343. 5. 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. <i>Iran J Pediatr.</i> 2014 Aug;24(4):352-8. 6. Desarno J, Sandate I, Green K, Chavez P. When in Doubt, Pull the Catheter Out: Implementation of an Evidence-Based Protocol in the Prevention and Management of Peripheral Intravenous Infiltration/Extravasation in Neonates. <i>Neonatal Netw.</i> 2018 Nov;37(6):372-377. 7. Hackenberg RK, Kabir K, Müller A, Heydweiller A, Burger C, Welle K. Extravasation Injuries of the Limbs in Neonates and Children—Development of a Treatment Algorithm. <i>Dtsch Arztebl Int.</i> 2021 Aug 23;118(33-34):547-554.

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	<ol style="list-style-type: none">8. Fidalgo P, Fabregat G, Cervantes A, et al. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. <i>Ann Oncol</i>. 2012 Oct;23 Suppl 7:vii167-73.9. Davies J, Gault D, Buchdahl R. Preventing the scars of neonatal intensive care. <i>Arch Dis Child Fetal Neonatal Ed</i>. 1994 Jan;70(1):F50-1.10. Sagheb S, Mohseni SO, Lamsehchi A. A new approach to skin extravasation injury management during the neonatal period. <i>BMC Pediatr</i>. 2022 Jul 26;22(1):45111. Bertelli G, Dini D, Forno GB, Gozza A, Silvestro S, Venturini M, Rosso R, Pronzato P. Hyaluronidase as an antidote to extravasation of Vinca alkaloids: clinical results. <i>J Cancer Res Clin Oncol</i>. 1994;120(8):505-612. Australian Injectable Drugs Handbook, 8th Edition (online) accessed 25/08/2022.13. Gopalakrishnan PN, Goel N, Banerjee S. Saline irrigation for the management of skin extravasation injury in neonates. <i>Cochrane Database of Systematic Reviews</i> 2017, Issue 7. Art. No.: CD008404. DOI: 10.1002/14651858.CD008404.pub3.14. Hyalase. MIMS Online. Accessed 15/12/2022.
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