# **Digital adrenaline injection injuries: A case series and review**

MW ElMaraghy MD<sup>1</sup>, AW ElMaraghy MD<sup>2</sup>, HB Evans MD FRCSC<sup>1</sup>

<sup>1</sup>Department of Plastic Surgery, University of Western Ontario, University Hospital, London, Ontario; <sup>2</sup>Department of Orthopaedic Surgery, University of Toronto, St Michael's Hospital, Toronto, Ontario

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Accidental digital adrenaline autoinjection is an uncommon injury, with only a few case reports existing in the literature. A six-case series of digital EpiPen injection injuries, a review of the literature and treatment protocols with their pathophysiological and pharmacological basis are presented. Oral nifedipine, topical 2% nitroglycerine paste, digital block using lidocaine and warm water immersion are ineffective in acutely reversing digital ischemia. Clinical and experimental evidence demonstrating spontaneous resolution of digital vasospasm may support the expectant management of these injuries. If medical intervention is undertaken, safe and rapid reversal of adrenaline-induced digital ischemia can be achieved with local and/or regional infiltration of phentolamine mesylate. Based on a review of the current case series and the literature, the authors' preferred method of treatment includes simultaneous digital block with a mixture of phentolamine and 2% lidocaine and local injection of phentolamine at the puncture site. Initially, the authors suggest using 5 mg phentolamine mesylate in 2 mL of 2% lidocaine, and injecting 1 mL (2.5 mg) of the solution into the ulnar and 1 mL (2.5 mg) into the radial aspect of the base of the involved digit, followed by injecting the injury site with a 5 mg/mL solution of phentolamine.

Key Words: Adrenaline, Finger, Injection, Ischemia, Phenotolamine

# Injection digitale d'adrénaline: revue et série de cas

**RÉSUMÉ :** L'autoinjection accidentelle d'adrénaline dans un doigt est relativement rare puisque seuls quelques cas ont été signalés dans la littérature. Le présent article propose six cas de lésions causées par l'injection digitale d'EpiPen, une revue de la littérature et des protocoles thérapeutiques et leur justification physiopathologique et pharmacologique. La nifédipine orale, la pâte de nitroglycérine topique à 2 %, le bloc digital à la lidocaïne et l'immersion dans l'eau chaude sont inutiles pour renverser l'ischémie digitale aiguë. Les preuves cliniques et expérimentales de la résolution spontanée du vasospasme digital pourraient appuyer une attitude attentiste face à de telles lésions. Si l'on préfère intervenir, une résolution sûre et rapide de l'ischémie digitale provoquée par l'adrénaline est possible au moyen d'infiltrations locales ou régionales de mésylate de phentolamine. Sur la base d'une revue de la présente série de cas, la méthode thérapeutique préférée des auteurs a été le bloc digital au moyen d'un mélange phentolamine et lidocaïne à 2 % et l'injection locale de phentolamine au point d'injection. Initialement, les auteurs suggèrent l'emploi de 5 mg de mésylate de phentolamine dans 2 mL de lidocaïne à 2 %, et l'injection de 1 mL (2,5 mg) de la solution sur la face cubitale et 1 mL (2,5 mg) sur la face radiale de la base du doigt atteint, suivie d'une injection de solution de phentolamine à 5 mg/mL au site atteint.

A drenaline is an endogenous catecholamine and a potent agonist of alpha and beta adrenergic receptors (1). It is a powerful vasopressor, and one of its many established clinical uses is in the treatment of anaphylactic allergic reactions

(1,2). Approximately 80,000 commercial autoinjection units (EpiPen, Center Laboratories, New York) have been sold each year since 1980 (2). These units are designed to deliver 0.3 mg of 1:1000 adrenaline solution subcutaneously by pressing the injector end of the pen into a suitable location. The manufacturer reports one accidental injection per 50,000 units annually. These uncommon autoinjection injuries generally

Correspondence: Dr MW ElMaraghy, 62 Tetherwood Boulevard, London, Ontario N5X 3W2.

involve the inadvertent application of digital pressure on the injection apparatus while demonstrating use of the unit. This results in a critically ischemic digit with minimal systemic absorption of the significant local dose of adrenaline.

Extravasation of intravenous adrenaline infusion has been previously documented (3). Isolated case reports of accidental digital autoinjection exist in the emergency medicine literature (2,4-9); however, there have been no reports of digital adrenaline-induced vasospasm in the hand surgery literature.

We present six cases of accidental digital adrenaline autoinjection, and different treatment protocols with their pathophysiological and pharmacological basis. To our knowledge, this represents the only such case series in the literature to date.

## CASE PRESENTATIONS

#### Case 1

A 49-year-old, left hand dominant female presented approximately 3 h after accidental discharge of an EpiPen into the pulp of her right index finger. Despite immediate submersion in warm water, her finger became painful, cold, white and insensate within an hour, but she had no systemic complaints. Examination confirmed a cold, blanched digit with absent capillary refill and decreased sensation to the level of the metacarpal-phalangeal (MCP) flexion crease. Treatment was initiated with a mixture of phentolamine mesylate 0.5 mg (0.1 mL), and lidocaine 2% (1 mL) to a total volume of 1.1 mL, injected on either side of the base of her index finger using a standard digital-block technique. Immediate return of capillary refill was noted from the MCP to the proximal interphalangeal (PIP) flexion crease. The injection was repeated after 1 h and was accompanied by further improvement to the distal interphalangeal (DIP) flexion crease. After a third treatment 1 h later, and 3 h after initiation of treatment, her entire finger had regained its vascularity. At follow-up, the patient was asymptomatic with no evidence of tissue necrosis.

#### Case 2

A 55-year-old right hand dominant female nurse presented approximately 4 h after self-injection with an EpiPen, just distal to the volar PIP flexion crease of her right index finger. Her digit immediately became cold, pale and lost sensation. Examination confirmed a critically ischemic digit to the level of the MCP flexion crease. She experienced systemic symptoms including tachycardia and palpitations, and was admitted to hospital for observation and treatment. She was treated with continuous hot compresses, topical 2% nitroglycerine paste repeated every 2 h and a digital block of lidocaine 2%. Two-and-a-half hours after initiation of treatment, return of colour was noted to the level of the DIP flexion crease, followed by improvement to the level of the PIP flexion crease at 5.25 h. At 9.5 h post presentation and 13.5 h post injury, normal colour and sensation had been restored. Although at one month follow-up no deficits could be demonstrated, she reported persistent pain in her forearm, which she attributed to the injury. It is noteworthy that a work compensation claim was made with respect to this injury, and she was delayed in her return to work.

### Case 3

A 42-year-old right hand dominant female presented with a 'cold' thumb 6 h after accidental EpiPen injection of the pulp of the left thumb. She had unsuccessfully attempted to treat her thumb by immersion in warm water. On examination, pallor extended proximal to the interphalangeal flexion crease. It is unclear how much of the 0.3 mg of 1:1000 adrenaline solution was delivered. She had slower, but preserved capillary refill in the thumb pad, associated with normal two-point discrimination. Treatment with nifedipine 10 mg orally was given 15 mins after presentation. The patient was sent home 2 h later with instructions to return if pallor persisted. Warmth and tingling in the thumb, normal colour and capillary refill was restored 9.5 h after initiation of treatment and 15.5 h after the initial injury.

#### Case 4

A 19-year-old, right hand dominant female autoinjected her left index finger volar to the DIP flexion crease. She presented 20 mins later with a blanched, painful finger. Forty mins after injury, treatment was initiated with phentolamine 0.5 mg (0.1 mL) injected into the ulnar digital pulp and 0.5 mg (0.1 mL) into the radial digital pulp. At 15 mins after injection, the finger was pink to the level of the DIP flexion crease, but remained pale proximally to the level of the MCP. Repeat injection was performed using phentolamine 0.5 mg (0.1 mL) proximal to the DIP flexion crease volarly. Half an hour after initiation of treatment, the entire finger was pink and asymptomatic.

#### Case 5

A 44-year-old male physician autoinjected his right dominant thumb pulp, but did not seek medical attention despite immediate pain and pallor. Within 2 h, capillary refill had returned to the proximal portion of the thumb. Within 10 h complete restoration of vascularity was observed without medical intervention. No long term sequelae were noted.

#### Case 6

A 25-year-old female presented with palpitations and pain in the right long finger after accidental discharge of an EpiPen into the volar aspect of the middle phalanx of the involved digit. Digital block was performed using phentolamine 2 mg (2 mL) on each of the radial and ulnar aspects of the long finger (total of 4 mg). Within 30 mins, the finger was pink from the web space to the mid-middle phalanx. The tip of the finger remained pale. Repeat injection of phentolamine 2.5 mg (0.5 mL) locally into the previous adrenaline injection site resulted in return of vascularity to the fingertip. Return of vascularity of the entire finger was re-established within 40 mins of initiation of treatment.

# DISCUSSION

Adrenaline's effects are attributable to stimulation of both alpha and beta-adrenoreceptors, and include central nervous alertness, tachypnea, increased blood pressure through chronotropic and ionotropic action, and intense peripheral vasoconstriction (1). Studies of perivascular smooth muscle in human digital arteries have demonstrated the presence of alpha-1 and alpha-2 postsynaptic adrenoreceptors linked to the same postreceptor effector mechanisms of calcium entry via voltage operated channels (10). Both alpha-1 and alpha-2 receptors are of equal potency and cause profound vasoconstriction when stimulated (10-13).

Adrenaline has been used in concentrations of 1:200,000 to 1:100,000 to prolong the effect of local anaesthetics via vascular bed vasoconstriction and to control bleeding during wound repair. Classical teaching has warned against the use of adrenaline injection in areas where blood supply may be compromised such as the fingers, toes, nose, ears and penis (14). However, to our knowledge, no report exists in the literature documenting digital necrosis secondary to adrenaline injection.

Proposed treatment options for digital ischemia have included digital sympathectomy (digital block, surgical), systemic or topical nitroglycerine, systemic or topical calcium channel blockers (nifedipine), local/regional infiltration of phentolamine and proximal intra-arterial injection of phentolamine.

Digital artery sympathectomy has been described as a technique for treatment of vascular insufficiency of digits (15). Digital arteries receive anywhere from three to 12 sympathetic twigs from the median and ulnar nerves. Surgical sympathectomy is performed by removal of proper digital artery adventitia over a length of 3 to 4 mm (15). A simpler, although temporary, method of sympathectomy may be achieved chemically using perivascular infiltration of a local anaesthetic block. In a rat model, topical 20% lidocaine reversed adrenaline induced arterial spasm in 30 to 45 mins, while a 2% concentration was ineffective (16). The specific mechanism of action on the cell membrane is unknown; however, lidocaine affects ion flux in both nerve and smooth muscle cell membranes (16). This is a direct vascular effect, independent of digital sympathetic innervation.

Nitroglycerine is an endothelium-independent smooth muscle relaxant that acts through the intracellular formation of nitrosothiols, leading to accumulation of guanosine 3'-5'-cyclic monophosphate (17). Subsequent production of a protein kinase leads to dephosphorylation of the light chain of myosin and relaxation of smooth muscle. Topical nitroglycerine can decrease adrenaline-induced vasospasm in animal models (17). Nitroglycerine ointment has been shown experimentally to improve random skin-flap survival in animal models (18), and has been used clinically to treat dopamine extravasation neonates (19).

Calcium channel blockers, such as nifedipine, act by selective inhibition of  $Ca^{2+}$  influx through the cell membrane, lowering myoplasmic levels of  $Ca^{2+}$  and preventing the phosphorylation of actin and myosin, causing smooth muscle relaxation (16). In a rat tail artery model, topical nifedipine at the highest soluble concentration  $(10^{-3} \text{ M})$  had no effect on adrenaline-induced vasospasm (16); however, in human digital arteries concentrations of  $10^{-8}$  to  $10^{-7}$  M have demonstrated inhibition of noradrenaline-induced spasm (13). The systemic use of nifedipine causes vasodilation (16); however, its role in the treatment of adrenaline-induced digital arterial spasm is unknown.

Phentolamine is a short-acting, reversible, competitive inhibitor of both alpha-1 and alpha-2 adrenergic receptor subtypes (20,21). Hypotension, reflex tachycardia, arrhythmias and cardiac ischemia are the main side effects of systemic use of phentolamine. These adverse effects are avoided by local/regional infiltration of low doses of phentolamine. Intravenous administration of medications are complicated by extravasation into the interstitial tissues in 22.8% of treatments (3). When the medication has vasoconstrictor properties, such as noradrenaline or adrenaline, it has been reported that either local infiltration (22) or proximal intra-arterial phentolamine mesylate is the treatment of choice, and may abort tissue necrosis (3,11,23).

Intra-arterial injection of phentolamine has been shown to reverse human digital artery vasospasm (24,25). Similarly, compared with other vasodilators, including nitroglycerin, phentolamine was the most effective at reversing clonidine-induced digital vasospasm (23). In a rat tail artery model, topical phentolamine ( $10^{-2}$  M or 3.8 mg/mL phentolamine mesylate) resulted in complete relief of adrenaline-induced vasospasm in an average of 60 to 75 mins (16).

Seven case reports of accidental digital adrenaline autoinjection have been presented in the peer reviewed literature (2,4-9).

Case 5 served as a control in the present series, in that he received no medical treatment, and still had complete restoration of perfusion within 10 h with no long term sequelae.

Warm water immersion, oral nifedipine and topical 2% nitroglycerine paste combined with a digital block using 2% lidocaine were ineffective in acutely reversing the digital ischemia. These interventions required approximately 9.5 h to demonstrate restoration of digital perfusion and likely did not alter or improve the clinical course of untreated digital adrenaline injection. These findings are consistent with those of previous investigators who also noted a lack of response to warm water (6,8), digital block (5,6), topical nitroglycerine (5,6,8) and oral nifedipine (8).

Local infiltration of phentolamine into the puncture site has been used successfully by Hinterberger and Kintzi (6), Mol and Gaver (8), McCauley et al (5), and Deshmukh and Tolland (4). The total dose of phentolamine varied from 1 to 10 mg, and concentration varied from 1 to 5 mg/mL (4,6). The total volume injected was between 1 and 2 mL (4,6); however, some authors did not specify the concentration or volume of phentolamine injected (5,8). Resolution of ischemia was noted between 20 and 60 mins, and did not require repeat injections.

Review of case four demonstrates similar efficacy of local

infiltration of phentolamine, which reversed the digital ischemia in approximately 30 mins. Phentolamine 1 mg in 0.2 mL was used initially; however, a second injection proximally of 0.5 mg in 0.1 mL was required to restore perfusion proximal to the DIP flexion crease. Hinterberger and Kintzi (6) also injected phentolamine proximal to the EpiPen puncture site, at the 'line of ischemia' or demarcation.

The successful use of regional phentolamine infiltration using digital block technique has also been reported by Maguire et al (2), and Burkhart (7). Maguire et al used 2 mL of 0.25 mg/mL phentolamine and 1% lidocaine at each side of the base of the involved digit. This was repeated at 15 mins, and complete restoration of perfusion was noted at 30 mins (total dose of 2 mg). Burkhart used 1 mL of 0.5 mg/mL phentolamine and 1% lidocaine in a similar manner. This was repeated at 1 h using another 2.5 mg of phentolamine with complete resolution of digital ischemia (total dose of 3.5 mg).

Similarly, case one demonstrated reversal of digital ischemia using regional infiltration of phentolamine and 2% lidocaine, using digital block technique, which required approximately 3 h – significantly longer than previously described using similar technique (2,7). This discrepancy was due largely to a delay of 1 h between each of the three injections. It should also be noted that a lower total dose and concentration of phentolamine was used per digital injection.

Markovchick and Burkhart (9) combined regional and local phentolamine injection. Initially, digital block technique was used followed by local infiltration for persistent pulp ischemia. Case six demonstrated the use of the same technique with similar outcome.

No adverse reactions or systemic side effects have previously been reported after the local/regional infiltration of phentolamine in doses as high as 10 mg. Local/regional injection of phentolamine was safely used in the present case series.

#### CONCLUSIONS

Review of the efficacy of various treatment modalities used in the management of the current case series poses interesting questions about the management of these uncommon injuries. Do digital adrenaline injection injuries require any medical intervention? Animal experimental evidence using rat tail arteries exposed to 1 mL of topical 1:1000 adrenaline demonstrated partial resolution of vasospasm as early as 3 h after exposure, and complete resolution as early as 12 h without treatment (16). In the current case series, spontaneous resolution of vasospasm within approximately 10 to 15 h has been observed, without long term sequelae (cases two, three

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and five). Clinically, local anaesthetics with 1:200,000 concentration of adrenaline have long been used in the hand and digits without untoward effects (26). The above observations may support the expectant management of digital adrenalineinjection injuries.

Safe and rapid reversal of adrenaline-induced digital ischemia can be achieved with local and/or regional infiltration of phentolamine mesylate.

If treatment using local injection of phentolamine is undertaken, great care must be exercised to prevent a pressureinduced exacerbation of digital ischemia, due to the volume of injection. We recommend using a 5 mg/mL solution of phentolamine mesylate injected using a 25 gauge needle into the injury site and proximally (6) (case 4). The effectiveness of this concentration is supported by an experimental model (16), and optimizes the dose to volume ratio. Total dose will be limited by the volume that can be injected while maintaining finger pulp tension to a minimum. This is an empirical judgement based on clinical experience. Reassessment of vascularity should be performed within 15 to 30 mins, and repeat injection performed as necessary.

Regional infiltration using digital block technique avoids the concern of digital pressure-induced vascular compromise, and will provide the patient with analgesia. We suggest using a solution of 5 mg phentolamine mesylate in 2 mL 2% lidocaine, and injecting 1 mL (2.5 mg) of the solution into the ulnar and 1 mL (2.5 mg) into the radial aspect of the base of the involved digit. This should be repeated every 15 to 30 mins as required.

The authors' preferred method of treatment includes simultaneous digital block with a mixture of phentolamine and 2% lidocaine and local injection of phentolamine at the puncture site. Initially, we suggest using 5 mg phentolamine mesylate in 2 mL 2% lidocaine, and injecting 1 mL (2.5 mg) of the solution into the ulnar and 1 mL (2.5 mg) into the radial aspect of the base of the involved digit. After the onset of analgesia due to the digital block, this should be followed by injecting the injury site with a 5 mg/mL solution of phentolamine mesylate. The total volume of local phentolamine mesylate will be limited by the finger pulp tension. Repeat injection will not likely be required using this technique; however, reassessment of vascularity should be performed within 30 mins, and repeat injections performed as necessary. No safe maximal dose of local/regional phentolamine injection has been defined. If total doses in excess of 10 mg are required, hemodynamic monitoring should be considered.

Recalcitrant ischemia may necessitate intra-arterial phentolamine administration as described by Coffman et al (24) and Arneklo-Nobin et al (25).

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