

Six Years of Epinephrine Digital Injections: Absence of Significant Local or Systemic Effects

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Study objective: Epinephrine autoinjectors are known to result in accidental digital injections. Treatment recommendations and adverse outcomes are based on case reports. The objective of our study is to determine the frequency of digit ischemia after epinephrine autoinjector digital injections. In addition, we describe the frequency of epinephrine digital injections, treatments used, adverse local effects, and systemic effects.

Methods: We performed a retrospective cohort study on cases reported to 6 poison centers during 6 years, using a search of the Texas Poison Center Network database. Patients who had an epinephrine injection of the hand were reviewed, and digital injections were included. Variables collected included demographics, local and systemic effects, symptom duration, treatments used, comorbidities, and whether admission, surgery, or hand surgery consultation was used. One trained abstractor used a standard electronic data collection form.

Results: There were 365 epinephrine injections to the hand identified for the 6-year period. Of these, 213 were digital injections, and 127 had follow-up. All patients had complete resolution of symptoms. None of the patients were hospitalized or received hand surgery consultation or surgical care. Significant systemic effects were not reported. Pharmacologic vasodilatory treatment was used in 23% (29/127) of patients. Ischemic effects were documented for 4 patients, and 2 of these had symptom resolution within 2 hours. All 4 patients received vasodilatory therapy and were discharged home, with complete resolution of symptoms.

Conclusion: In our series of patients using poison center calls about digital epinephrine autoinjections, there were no cases in which clinically apparent systemic effects were recorded and few patients had ischemia. No patient was admitted or had surgery. Most clinicians did not use vasodilation medications or techniques. [Ann Emerg Med. 2010;xx:xxx.]

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INTRODUCTION

Background

The incidence of anaphylaxis in children and adults has increased, resulting in an increased use of epinephrine autoinjectors for treatment.^{1,2} An epinephrine autoinjector is the mainstay of outpatient therapy for anaphylaxis and severe allergic reactions.² Accidental epinephrine digital injection by autoinjector is a known risk of these dispensing units.³

Importance

Textbooks and references note digit ischemia as a concern when epinephrine is used in the digit, particularly in concentrated forms.^{4-9p636} Treatment recommendations vary and are based on case reports and a collection of small case series, focusing on using local vasodilatory treatment. Local

phenolamine injection, topical nitroglycerin paste, and terbutaline are treatments that have been reported.¹⁰⁻¹⁶

Based on the lack of toxicity of digital injection epinephrine with local anesthetics for hand lacerations, observation of epinephrine digital injections without local vasodilatory treatment has been recommended.¹⁶⁻¹⁸

Goals of This Investigation

We sought to determine the frequency of digit ischemia after autoinjector epinephrine digital injections. In addition, we describe the frequency of epinephrine digital injections, treatments used, adverse local effects, and systemic effects of cases reported to 6 poison centers during a 6-year period.

MATERIALS AND METHODS

Study Design

We performed a retrospective cohort study approved by our institutional review board.

Editor's Capsule Summary

What is already known on this topic

Once considered dangerous, digital injection of epinephrine is safe, according to clinical reports throughout the past decade. Clinical practice has been slow to change.

What question this study addressed

The authors describe the outcome of epinephrine autoinjector incidents for which a poison center was contacted.

What this study adds to our knowledge

This retrospective analysis of 127 patient records in a poison center database found few incidents of ischemia or systemic effects after digital injection. Outcomes were uniformly favorable.

How this might change clinical practice

In most cases, epinephrine autoinjector incidents involving the digits may be observed. Because autoinjectors contain more epinephrine than typically used in wound preparation for suturing, the practice of using lidocaine with epinephrine is reasonable.

Setting and Selection of Participants

The Texas Poison Center network receives spontaneous telephone calls from patients and health care providers. The network is composed of 6 poison centers that provide clinical consultative services throughout Texas 24 hours per day. Each call is received by trained nurses or pharmacists for the purpose of managing the exposure and documenting the consultation. All cases are recorded in a nationally standardized data collection form and uploaded to the national poison center database every 20 minutes. This form and database are maintained by the American Association of Poison Control Centers. Cases are followed until the outcome of the event is known. Medical toxicologists are available for consultation on complex cases. If a patient is not referred to a health care facility, the poison specialist will call the patient back in 1 to 3 hours to obtain follow-up and determine resolution of symptoms. If the patient goes to the hospital, the specialist continues to follow the case by telephone and collects medical information and course from the patient's provider.

We searched 6 years of data (2000 to 2005) in the Texas Poison Center Network (Thomson Reuters, Greenwood Village, CO) for EpiPen autoinjector, EpiPen Jr. Autoinjector, EpiPen solution, EpiPen Jr. solution, Ana-Kit, and Twinjet to identify all American Association of Poison Control Center generic codes and POISINDEX product identification codes for epinephrine autoinjectors. We also used "epinephrine" as a generic search term, combined with "parenteral." All hand

exposures were reviewed, and only finger injections were included. All ages were included. Both adult (0.3 mg) and junior (0.15 mg) autoinjectors were included. The advice provided by our staff was guided by training and clinical experience. The Texas Poison Center Network does not have a standard clinical protocol for these exposures.

Data Collection and Processing

Symptoms, signs, treatments, and outcomes were extracted from the database through chart review of the clinical notes and coded diagnoses and treatments. Outcomes were coded as "no effect," "minor," "moderate," "major," and "death," according to the American Association of Poison Centers National Poison Data System outcome criteria.¹⁹ "No effect" indicates that the patient did not develop any signs or symptoms because of the exposure. "Minor effects" are signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly, with no residual disability or disfigurement. "Moderate effects" are signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life threatening, and the patient had no residual disability or disfigurement. "Major effects" are signs or symptoms as a result of the exposure that were life threatening or resulted in significant residual disability or disfigurement (eg, repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, disseminated intravascular coagulation). "Death" indicates that the patient died as a result of the exposure or as a direct complication of the exposure. Our network is made of 6 poison centers and calls are received and documented by trained poison information specialists. They enter clinical notes and document standardized codes for common symptoms, signs, and treatments. Free text clinical notes are also entered.

We saved the charts electronically and then printed and reviewed them. Two trained abstractors (A.E.M. and a research associate) abstracted each chart and entered the data into a secure spreadsheet. The abstractors reviewed the clinical notes for symptoms, signs, and treatments not coded. One of the investigators (V.S.B.) trained the abstractors. The abstractors trained on 50 charts not included in the study cohort. They were given feedback on data abstraction and corrected mistakes. The standard data collection tool was devised before this run-in period, and it was revised before the chart review began.

We defined ischemia as "ischemia," "ischemic," "necrosis," "necrotic," "black," "blue," "cold," sustained poor capillary refill, or symptoms lasting more than 8 hours, as noted in the chart or clinical note. For a discrepant case, 2 authors reviewed the case and determined whether ischemia was present to ensure the broadest capture of cases. Other data collection variables included demographics (age, sex), exposure reason, body location of injection, possible symptoms and signs of ischemia (pain, discoloration, blanching, swelling, poor capillary refill, and numbness), treatments, systemic effects, symptom duration,

residual symptoms, comorbidities (vascular disease, diabetes, episodic, symmetric acral vasospasm (Raynaud's), thromboangiitis obliterans (Burger's), vasculitis, peripheral neuropathy, or concomitant trauma), and disposition. The National Poison Data System defines tachycardia as a pulse rate greater than 100 beats/min, and it defines hypertension as diastolic blood pressure greater than 90 mm Hg.²⁰ We applied age-related standards for children.²⁰ A complete resolution of symptoms was defined as resolution of all symptoms before emergency department disposition or hospital discharge. Definitions and outcomes were defined before abstraction. We performed double extraction on all charts, and agreement was measured. Any discrepancies were resolved by an investigator (V.S.B.).

Outcome Measures

Our primary outcome was incidence of ischemia after epinephrine digital injection. The outcome of ischemia was included if noted in the "Clinical Effects" categories or "Notes" section of the database collection form. Our secondary outcomes were frequency of epinephrine digital injections, treatments used, adverse local effects, and systemic effects.

Complete resolution of symptoms was determined by 2 methods. The majority of resolutions were noted in the "Clinical Effects" category. If not explicitly noted, we reviewed the category "Clinical Effects Duration." If symptoms resolved within 8 hours and the clinical notes were consistent with resolution, the cases were also considered to have "complete resolution of symptoms." If neither of these fields was completed, we assumed the patient did not follow up and the patient was not included in the study.

Primary Data Analysis

All data were entered into a password-protected electronic spreadsheet (Microsoft Excel; Microsoft, Redmond, WA). We performed descriptive statistics.

RESULTS

Main Results

Of 365 reported hand epinephrine injections, 213 involved a digit, and 127 cases had complete follow-up (Figure). Of patients with follow-up, the mean age was 21.5 years (median 14.5 years; range 8 months to 69 years). Eighteen (14%) patients were younger than 6 years; 48 (38%) were younger than 12 years. Half were male patients (49.6%). Sixty-eight cases (54%) were managed at home or in non-health care facilities (school or work), and 62 of these had minor effects. All patients had complete resolution of symptoms. Most cases (58%) had less than 2 hours of symptoms (Table 1). No effects were reported in 10% (12/127). Minor effects were reported in 77% (98/127), moderate effects in 13% (16/127), and major effects in 1 case. The patient reported to have major effects had complete resolution of symptoms, had no systemic effects, and was discharged home from the health care facility. No patient was admitted, received hand surgery consultation, or had surgical care.

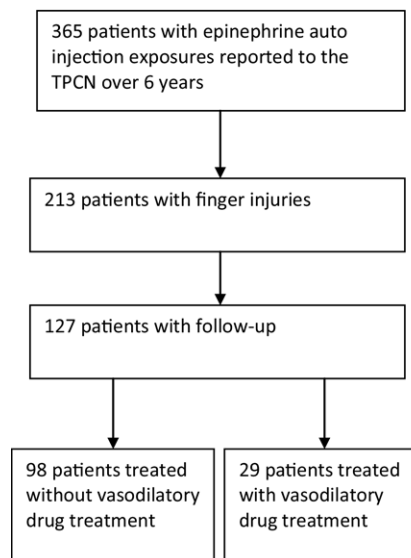


Figure. Flow diagram of patients entered into the study. TPCN, Texas Poison Control Network.

Table 1. Incidence of local symptoms in 127 patients with digital epinephrine autoinjector exposure.

Local Symptoms	Number (%), N=127
Pain	86 (68)
Blanching	53 (42)
Discoloration	21 (17)
Numbness	20 (16)
Ecchymosis	4 (3.1)
Ischemia	4 (3.1)
Decreased capillary refill	2 (1.6)

Table 2. Medical vasodilatory treatments in 127 patients with digital epinephrine autoinjector exposure.

Treatment	Number of Cases (%), N=127
No drug therapy	98 (77)
Nitroglycerin paste	19 (15)
Phentolamine	7 (6)
Nitroglycerin and phentolamine	2 (1.6)
Terbutaline	1 (0.8)

No significant systemic effects and no vascular-related comorbidities were reported. Six patients had transient tachycardia and 1 had palpitations, but no pulse rate was documented in the clinical notes. Hypertension was not documented in any case. Treatment for systemic effects was not documented in any case.

Drug treatment was used in 29 of 127 cases (23%): 19 topical nitroglycerin paste, 7 local phentolamine injection, 2 nitroglycerin paste and phentolamine, and 1 local terbutaline (Table 2). Eight of the 98 patients without pharmacologic vasodilatory therapy had moderate effects. All had complete resolution of symptoms. Warm soaks alone were used in 32% (40/127) of cases. All patients in this group also had complete resolution of symptoms.

Table 3. Summary of 4 cases (N=127) of digital ischemia in patients with digital epinephrine autoinjector exposure.

Case	Symptoms	Ischemic Symptoms	Treatment	National Poison Data System Clinical Outcome	Duration of Symptoms, h
1	Pain, blanching, numbness, poor capillary refill	"Turned blue," "blanched"	Phentolamine	Moderate	>8 and ≤24
2	Blanching, discoloration, numbness	"Gray," "severe vasoconstriction," poor capillary refill	Phentolamine	Moderate	<2
3	Blanching, poor capillary refill	"Ischemic," "cold"	Phentolamine and nitroglycerin	Minor	<2
4	Pain, blanching	"Cold," "necrosis"	Nitroglycerin	Moderate	>2 and ≤8

Of the 127 patients with follow-up, 4 (3.1%) patients were reported to have an "ischemic" finger (Table 3). All patients had a complete resolution of symptoms and were discharged home. Two patients had resolution within 2 hours of injection. All patients received medical therapy.

κ For the 2 abstractors for "complete resolution of symptoms" was 0.82 (95% confidence interval [CI] 0.64 to 0.99), 0.79 (95% CI 0.51 to 1) for ischemia, and 1.0 for treatment used.

LIMITATIONS

Our study is a retrospective database review and contains the inherent limitations. However, we attempted to mitigate the retrospective study design flaws with strict methodology, using a trained abstractor, holding periodic meetings, using a standardized data form, and measuring interrater agreement.²¹ Our study is also limited by the use of Texas Poison Center Network records and strict categories for clinical effects. Only patients and providers who called the poison center were evaluated, possibly limiting the spectrum of cases reviewed. Patients may have visited a health care facility and not called a poison center. Some of these patients may have had ischemia or required surgical intervention. Hospital and clinic medical records were not available for review, limiting conclusions on systemic findings such as tachycardia and local examination findings such as ischemia. In addition, with poison center records we cannot be certain examination findings, abnormal vital signs, and treatments were not missed. As was done in other studies, we used the clinical effect categories listed by the poison control center, as well as the clinical notes, to determine outcomes and clinical course.²² Many patients had no follow-up after the initial consultation with the poison control center. Some of these patients may have had an adverse outcome, thus tempering the conclusion that ischemia does not occur from digital epinephrine injections. Finally, determining ischemia depended on an amalgamation of clinical notes; however, we attempted to capture all possible cases of ischemia with broad criteria to allow full review of each case.

DISCUSSION

The results of our study suggest that ischemia after digital epinephrine autoinjection is rare. All patients had complete resolution of symptoms, most resolved in 2 hours, and 77% of

patients had minor outcomes. Health care providers uncommonly use drug treatment for epinephrine injection. Despite textbooks and case reports recommending phentolamine, topical nitroglycerin paste, and terbutaline as potential treatments, most health care providers in our study used observation only.^{4,5,10-16}

Systemic effects, surgery, and hospital admission were not found. Our results suggest that acute epinephrine digital injection may be treated effectively with supportive care and observation only. Although the spectrum of our cases is limited to poison centers, and adverse effects may have occurred in unreported cases, to our knowledge our series is the largest published to date. Our results are consistent with those of recent case reports.⁴

There were 4 patients with possible ischemia. However, all were discharged home and 2 had resolution within 2 hours. All patients had complete resolution of symptoms, return of normal skin color, improvement of capillary refill, and absence of necrosis on reexamination. The 4 patients received drug treatment; thus, we could not exclude that ischemic effects responded to therapy. Efficacy of one treatment cannot be determined, because the ischemic patients received different treatments and because we did not have a sufficient number of nonischemic patients who received drug treatment to allow comparison.

The patients managed by observation only did well and did not have serious systemic symptoms or local residual effects. According to our study population, for patients with persistent or worsening pain or decreased capillary refill, it would be appropriate to follow their course closely for at least 2 hours after injection. If symptoms persist beyond 2 hours, a health care provider should evaluate the patient and consider medical treatment. We could not find a published report of persistent ischemia, infarction, or residual effects after an epinephrine autoinjector. Many reported cases resolved with medical treatment; however, these patients might have improved with time, as was the case with most of the patients in our study.

Although the local epinephrine dose is greater with an autoinjector (0.15 to 0.3 mg per dose) than a local anesthetic digital block (3 mL of 1% lidocaine with epinephrine contains 0.03 mg), our data are consistent with those of these large studies of lidocaine mixed with epinephrine and suggest that digital ischemia induced by epinephrine is rare.²³ A large multicenter prospective study evaluating the use of elective epinephrine in local anesthesia concluded that finger infarction

in elective low-dose epinephrine injection in the hand and finger is remote.¹⁸ Other studies of lidocaine mixed with epinephrine have shown similar results, confirming its safety.¹⁶ Our results are also congruent with those of a previous study that documented resolution of vasoconstrictive effects within 90 minutes of digit injection, as measured by color Doppler flow.²⁴

In conclusion, in a large case series reported to poison centers of healthy patients with digital epinephrine autoinjections, there were no cases in which clinically apparent systemic effects were recorded, and few patients had ischemia. No patient was admitted or had surgery. Most clinicians did not use vasodilation medications or techniques.

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Author contributions: AEM and VSB conceived the study. AEM, VSB, DJB, and DLM designed the study. DJB and DLM collected the data, AEM extracted the data, and VSB supervised the data collection. AEM drafted the article, and all authors contributed substantially to its revision. VSB takes responsibility for the paper as a whole.

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Editor's Capsule Summary *What question this study addressed:*

The authors describe the outcome of epinephrine autoinjector incidents for which a poison center was contacted. *What this study adds to our knowledge:* This retrospective analysis of 127 patient records in a poison center database found few incidents of ischemia or systemic effects after digital injection. Outcomes were uniformly favorable.