Safety of digital injections with epinephrine

A Review of the Literature

ABSTRACT

Introduction

The belief that injections of epinephrine into end-artery sites causes gangrene stems from 48 cases of digital gangrene after injections of local anesthetics, 21 of which involved the use of epinephrine. The true cause of gangrene in those patients remains unclear, as there were many confounding variables. Necrosis has not been documented with a commercial mixture of lidocaine and low-dose epinephrines. The purpose of this literature review is to examine the safety of digital epinephrine injections.

Clinical Question

Do digital epinephrine injections result in ischemia, necrosis or gangrene?

Search Methods

Studies selected for review were identified by a PubMed search with the key terms “epinephrine” AND “ischemia” AND (“finger” OR “digit”). The search was limited to articles published in English and to human trials, resulting in 34 articles.

Study Methods

Of the five studies reviewed, one was a double-blind randomized controlled trial, two were non-blinded prospective studies, and two were non-blinded retrospective studies. Each study had different patient populations, ranging from those presenting for surgeries of the digits, to accidental epinephrine injections from auto-injectors. Subjects were followed until complete symptom resolution or until rescue treatment was employed. Primary exposures taken into

consideration for this review include incidence of digital ischemia, necrosis, or gangrene, and digital perfusion.

Results

Digital injections of epinephrine were found to be generally safe. Although only one study provided statistics, no statistically significant difference in outcomes among patients injected with plain lidocaine to those injected with lidocaine and low-dose epinephrine was found. Of those injected with low-dose epinephrine, there were no cases or ischemia. In those injected with high-dose epinephrine, four patients experienced ischemia.

Conclusions

Digital injections of low-dose epinephrine can be used with minimal risk of ischemia, necrosis, or gangrene.

BACKGROUND

There is an established dogma that epinephrine should not be used in end-artery sites, such as digits, the penis, the tips of the nose, or earlobes, because of its vasoconstrictive effects. This idea is reinforced in major textbooks, suggesting that there is a high risk of ischemia leading to gangrene in these sites.

Before the 1950s, there were cases in which digital gangrene was reported after injections of procaine or cocaine with and without epinephrine.[1] However, of the 48 documented cases of digital gangrene, only 21 involved the use of epinephrine.[2] Of those, 17 used unknown concentrations based on manual dilution, and almost all involved other confounding variables, such as hot soaks, tight tourniquets, or infection. Additionally, expiration dates were not added to injectable medicines in the United States until 1978. Before that year, there are reports of a recall of batches of procaine that were found to be toxic,[3] producing necrosis with and without epinephrine, in well vascularized parts of the body.

When injected into a digit, epinephrine's strong properties as an α-adrenergic receptor agonist leads to activation of α-receptors in that digit's arteries, leading to vasoconstriction,[1,4] putting the digit in a low flow state.[3] Since digits can survive in the absence of blood supply for up to 42 hours as long as they are kept at physiological temperature[5], vasoconstriction with low-doses of epinephrine probably would not lead to necrosis or gangrene. Necrosis has not been documented with a commercial mixture of lidocaine and low-dose epinephrine.[1,6,7]

The importance of this controversy is three-fold. First, many procedures on the hand which require a bloodless field end up in the operating room for no reason other than that they need a tourniquet to provide the bloodless field for a duration that would be intolerable without general anesthesia.[7] Such procedures are often simple, and could be performed in the clinic or emergency room with local anesthesia. Elective hemostasis with epinephrine would provide the bloodless field required to eliminate the need for tourniquet and general anesthesia, thereby allowing these procedures to be performed outside of the operating room. This would mean less cost to the patient, and less risk from general anesthesia and tourniquet use. Second, toxicity can occur with local anesthetics if doses exceed the recommendations, or as an idiosyncratic response.[8] Vasoconstriction reduces blood flow, thus reducing systemic absorption, and prolonging the local effects of the anesthetic. This reduces the amount of anesthetic needed, and reduces the probability of cardiovascular and central nervous system toxicity. [6,9] Thirdly, there are many surgery-specific advantages to having an unsedated, awake patient, so that the patient can interact with the surgeon during the procedure.[7] The purpose of this literature review is to determine whether the use of epinephrine in digits leads to ischemia, necrosis or gangrene.

FOCUS OF REVIEW

CLINICAL QUESTION

Do digital epinephrine injections result in ischemia, necrosis or gangrene?

DATA SOURCES

Studies selected for review were identified via a PubMed search, with the key terms "epinephrine" AND "ischemia" AND ("finger" OR "digit"). The search was limited to articles

published in the English language and human trials. UpToDate and Google Scholar were used to find other data.

STUDY SELECTION

The PubMed search produced 34 articles, from which eight abstracts were reviewed that pertained to the study question. Articles were excluded if they were not available online or in the Duke stacks. Five articles were selected for further review and two were retained for background information.

STUDY DESIGN

The five articles reviewed included a double-blind randomized controlled trial, two single-arm non-blinded prospective studies, and two single-arm non-blinded retrospective studies.

Exposures included injections of local anesthetic with or without epinephrine, or injections of epinephrine into the digits. Subjects in each study were followed until resolution of symptoms or need for rescue treatment.

Although the overall goal of each study was to establish the safety of the use of epinephrine in digits, the methods of determining safety varied among the studies. Primary outcomes included digital ischemia, digital gangrene, digital perfusion, the need for phentolamine rescue, and the need for additional injection or tourniquet. Other outcomes measured included satisfactory wound healing, fingertip temperature, bleeding from surgical site, and real-time digital artery

blood flow. For the focus of this review, this paper will take into account the incidence of ischemia, necrosis, or gangrene, and digital perfusion.

Study design information is presented in Table 1.

PATIENT SELECTION

Recruitment

Study participants were recruited from presentation to emergency rooms or clinics with a need for digital injection of local anesthetic with or without epinephrine, or from calls to poison control centers regarding accidental digital injections of epinephrine.

Inclusion Criteria

Patients needing digital injections of local anesthetics for procedures ranging from finger surgeries to digital fracture reductions, and patients reporting accidental injections of high-dose epinephrine were included in the study.

Exclusion Criteria

Patients were excluded from a study if they had pre-existing problems with hand or digit ischemia, such as Raynaud's disease or diabetes mellitus. If baseline data could not be assessed for study procedures, or if followup was incomplete, patients were excluded as well.

DEMOGRAPHICS

Study sample sizes ranged from 60 to 3,110 participants, with between 31 and 1,340 digits exposed to epinephrine. A total of 1,667 digits were injected with epinephrine, including 1,663 fingers and 4 toes. The mean age in four studies ranged from 21.5 years to 71 years. Ranges listed were as follows: 15 years – 86 years, 1 day – 93 years, and 8 months – 69 years. Male to female ratios ranged from 1:1 to 6:1, although not all studies listed the distribution.

Demographic information is presented in Table 2.

METHODS OF MEASUREMENT

Ischemia, or local anemia due to mechanical obstruction of the blood supply, is in fact the desired effect of elective digital epinephrine injections. However, ischemia is also what is being assessed as a negative outcome of digital epinephrine use. Although the authors of the studies reviewed do not mention how they differentiate between the desired ischemic effect and the problematic ischemic effect, they use the term "ischemia" only in the context of the negative effect they wish to avoid. Thus, this literature review will use the terms "ischemia" or "ischemic" only in the context of that same undesired effect.

Outcomes were measured by assessing instance of digital ischemia, necrosis, or gangrene. The method used to assess these outcomes varied between the studies. Clinical judgement, a variety of testing methods, and a keyword search were used.

Clinical judgement was used to determine factors including ischemic status, finger infarction, necrosis, tissue loss, or satisfactory wound healing. Providers also used their judgement to determine whether phentolamine should be administered to reverse the symptoms of epinephrine-induced vasoconstriction.

Digital perfusion was assessed with a variety of methods.[6] Digital and brachial artery systolic blood pressures were measured and used to calculate a digital-brachial artery systolic blood pressure index; fingertip temperature was measured; and in a handful of patients, real-time digital artery blood flow was assessed with a Duplex scanner which measured internal diameter of the digital artery and the blood velocity.

Key terms were extracted from poison control databases to determine ischemia.[12] Terms searched for included "ischemia," "necrosis," "black," "blue," "cold," sustained poor capillary refill, or symptoms lasting more than 8 hours. "Complete resolution of symptoms" was defined as resolution of symptoms before hospital discharge or emergency department disposition.

SAFETY AND ETHICAL CONSIDERATIONS

Study procedures were reviewed and approved by the governing institutional review board in three studies.[7,10,11] Written informed consent was obtained from all subjects before participation in two studies.[6,10] The remaining studies did not make mention of informed consent or institutional review board approval. Adverse events included an occasional "bluish" finger, tachycardia, palpitations, pain, numbness, and poor capillary refill. All adverse events were transient and resolved completely.

STATISTICAL METHODS

The studies reviewed assessed subjects for digital ischemia, necrosis, and gangrene, or for digital perfusion. Some studies also looked at need for additional injections of local anesthesia or need for tourniquet. Only incidence of digital ischemia, necrosis, or gangrene, and digital perfusion were considered in this review.

One study[10] achieved randomization by blinding healthcare providers as to whether the patients were receiving digital injections of plain lidocaine or digital injections of lidocaine with epinephrine. That study measured p-values to compare the incidence of ischemia among the two groups. The remaining studies did not perform statistical analysis of their results, as they were single-arm studies.

RESULTS

Digital injections of epinephrine were generally safe among all studies reviewed. Only four cases of ischemia were noted, all of which had complete resolution of symptoms. Twenty-nine patients overall received treatment for symptoms,[11] including 19 administrations of nitroglycerine paste, 7 local injections of phentolamine, 2 administrations of both nitroglycerine paste and phentolamine, and 1 administration of local terbutaline. The majority of patients did not receive any form of treatment, even if they experienced symptoms from the injections. Digital perfusion persisted in all patients.

Of note, the only patients to receive treatment among those in the reviewed studies were those with accidental injections of high-dose epinephrine (1:1,000). No patient who received an

elective injection of low-dose epinephrine received treatment, and if any symptoms were experienced, all resolved completely.[1,6,7,10]

The only study performing statistical analysis[10] found no statistical difference (P=0.23) between outcomes in patients receiving digital injections of lidocaine with low-dose epinephrine compared to those receiving digital injections of plain lidocaine.

Results information is presented in Table 3.

STUDY STRENGTHS

The strengths of the studies reviewed included prospective design, multiple surgeons performing procedures, and varied procedures performed.

Prospective design allowed for close follow up of subjects and collection of data.[6,7,10] Randomization and blinding of both participants and providers decreased the chance for bias and reduced confounding variables.[10]

Having multiple providers perform procedures eliminates the chance that results varied based on the expertise of the provider, increasing the generalizability of the results.[1,7,10]

The variety in the procedures performed eliminates the chance that outcomes were based on the nature of the procedure being conducted, further increasing the generalizability of the results.[1,7,10]

STUDY LIMITATIONS

Studies reviewed were limited by a lack of randomization, lack of blinding, undefined duration of follow-up, and methods of patient selection.

A lack of randomization may have added a potential for bias.[1,6,7,11] Epinephrine was avoided in certain patients, possibly leading to selection bias and underestimation of the true incidence of necrosis.

Some of the patients, providers, and investigators,[1,6,7,11] were not blinded to whether patients were receiving plain anesthetic or anesthetic with epinephrine, potentially leading to bias.

Although studies reported follow-up until resolution of symptoms, that duration of follow-up was unclear in most cases. The majority of cases resolved within the same day of the procedure. It is unclear whether they all had follow-up at a later date to confirm that there were in fact no lasting symptoms due to the exposure to epinephrine.

Patients included based on poison control calls regarding accidental epinephrine injections to digits may have had less severe symptoms.[11] Patients with more severe symptoms may have gone straight to the emergency department without calling poison control, which would have underestimated poor outcome.

DISCUSSION

This literature review aimed to determine the safety of digital injections of epinephrine. Epinephrine's vasoconstrictive effects are desirable in many types of digital procedures. However, existing dogma preaches that vasoconstriction from digital injections of epinephrine leads to irreversible vasospasm, ischemia, necrosis, and gangrene.

The results of this review suggest that ischemia after digital injection of epinephrine is rare, and in the event that it does occur, is completely reversible with various treatment techniques. Necrosis and gangrene seem to have only theoretical risk.[10] There was no statistical difference among outcomes in patients receiving plain lidocaine compared to those receiving lidocaine with epinephrine.

Among the studies in this literature review, all cases of ischemia were resolved with the use of phentolamine, nitroglycerine paste, or terbutaline, without incidence of necrosis or gangrene. Of note, symptoms were only severe enough to require treatment among patients injected with high-dose epinephrine. Although treatment was needed only in a small number of patients, epinephrine should not be injected into a digit without understanding how to reverse its vasoconstriction with phentolamine or other approved reversal treatments. This is equivalent to providers needing an understanding of morphine rescue with naloxone prior to injecting morphine.[7]

There may be risks involved with injecting epinephrine into digits, but the advantages of its use are great. Digital epinephrine use would eliminate the need for tourniquet and thus the associated

risks of general anesthesia in many procedures on the hand. There would be a remarkable reduction in cost for patients if procedures were performed under local anesthesia in the clinic as opposed to general anesthesia in an operating room. Epinephrine prolongs the effects of local anesthesia, reducing the amount of anesthetic needed, thus reducing the potential for toxicity. In addition, there are multiple surgery-specific advantages to having an awake, unsedated patient.[7]

CONCLUSION

The studies reviewed showed that digital injections of epinephrine are not likely to cause necrosis or gangrene, and are generally safe when administered in low doses. This conclusion has important clinical relevance and can change the practice of anesthesia of digits. Larger controlled trials should be performed to assess the safety of epinephrine injections into end-artery sites other than digits, and in patients with impaired vascularity. Until these studies are completed, low-dose epinephrine should only be recommended for use in the digits of otherwise healthy patients.

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Table 1: Study Design

Author (year)	Design	Exposure	Primary outcome
Wilhelmi et al[10] (2001)	Double-blind randomized controlled trial	1% lidocaine with 1:200,000 epinephrine	Need for additional injection, need for tourniquet, and complications including digital gangrene
Sylaidis et al[6] (1998)	Prospective, non-blinded	2% lidocaine with 1:80,000 adrenaline	Digital perfusion
Lalonde et al[7] (2005)	Prospective, non-blinded	Lidocaine or bupivacaine with 1:100,000 epinephrine or less	Digital ischemia and incidence of phentolamine rescue
Firoz et al[1] (2009)	Retrospective, non-blinded	Buffered 0.5% lidocaine with 1:200,000 epinephrine	Digital ischemia or necrosis ("satisfactory wound healing")
Muck et al[11] (2010)	Retrospective, non-blinded	1:1,000 epinephrine	Digital ischemia

Table 2: Demographics

Author (year)	Sample size	Digits exposed	Mean age (age distribution)	Gender (male / female)
Wilhelmi et al[10] (2001)	60	31	---	---
Sylaidis et al[6] (1998)	100	106	38 y (15y – 86y)	86 / 14
Lalonde et al[7] (2005)	3,110	1,340	53 y (1d – 93y)	---
Firoz et al[1] (2009)	63	63	71y	30 / 33
Muck et al[11] (2010)	365	127	21.5y (8m – 69y)	181 / 184

Table 3: Results

Author (year)	Group	Digits exposed	Incidence of ischemia, necrosis, or gangrene	% with ischemia, necrosis, or gangrene	p-value	Treatment received	Comorbid conditions
***Wilhelmi et al*[10] (2001)**	Anesthetic with epinephrine	31	0	0%	0.23	None	Not mentioned
	Anesthetic only	29	0	0%		None	Not mentioned
***Sylaidis et al*[6] (1998)**	Anesthetic with epinephrine	106	0	0%	Not reported	None	Not mentioned
***Lalonde et al*[7] (2005)**	Anesthetic with epinephrine	1,340	0	0%	Not reported	None	Not mentioned
***Firoz et al*[1] (2009)**	Anesthetic with epinephrine	63	0	0%	Not reported	None	33% circulatory disorders; 3% smokers; 64% hypertension; 29% type 2 diabetes; 51% taking anticoagulation
***Muck et al*[11] (2010)**	Epinephrine only	127	4	3%	Not reported	19 nitroglycerine paste; 7 local phentolamine injection; 2 nitroglycerin paste and phentolamine; 1 local terbutaline; 98 none (77%)	Vascular disease; Diabetes; Raynaud's disease; Burger's disease; Vasculitis; Peripheral neuropathy; Concomitant trauma