A Critical Look at the Evidence for and against Elective Epinephrine Use in the Finger

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Background: Medical texts continue to perpetuate the belief that epinephrine should not be injected in fingers. Little attention has been paid to analyze the evidence that created this belief to see whether it is valid. The significance is that elective epinephrine finger injection has been shown to remove the need for a tourniquet, and therefore delete sedation and general anesthesia for much of hand surgery.
Methods: All of the evidence for the antiadrenaline dogma comes from 21 mostly pre-1950 case reports of finger ischemia associated with procaine and cocaine injection with epinephrine. The authors performed an in-depth analysis of those 21 cases to determine their validity as evidence. They also examined in detail all of the other evidence in the literature surrounding issues of safety with procaine, lidocaine, and epinephrine injection in the finger.
Results: The adrenaline digital infarction cases that created the dogma are invalid evidence because they were also injected with either procaine or cocaine, which were both known to cause digital infarction on their own at that time, and none of the 21 adrenaline infarction cases had an attempt at phentolamine rescue.
Conclusions: The evidence that created the dogma that adrenaline should not be injected into the fingers is clearly not valid. However, there is considerable valid evidence in the literature that supports the tenet that properly used adrenaline in the fingers is safe, and that it removes the need for a tourniquet and therefore removes the need for sedation and general anesthesia for many hand operations. (*Plast. Reconstr. Surg.* 119: 260, 2007.)

It continues to be taught in medical schools and written in surgical textbooks[1–4] that epinephrine should never be injected into the fingers, toes, ears, and nose. It is not surprising that medical students are often confused when they see plastic surgeons regularly injecting low-dose (1:100,000) epinephrine into noses and ears. It is even more confusing to them that hand surgeons disagree among themselves about the safety and value of elective epinephrine injection into the finger.

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Medical students are taught by one group of surgeons that epinephrine should never be injected into the finger. These teachers quote the texts stating that digital infarction will occur because the finger is an end artery system and vasospasm there will be irreversible.

Medical students see another group of surgeons who regularly use epinephrine in the hand and finger. These surgeons are teaching the students that there is a serious body of evidence that epinephrine is safe to use in the hand. They believe that using epinephrine vasoconstriction in the hand and finger has permitted them to delete the tourniquet, and therefore to delete the risks and inconveniences of general anesthesia or sedation for most hand operations, such as flexor tendon repair, Dupuytren's contracture, and so forth.

In these days of evidence-based medicine, it is timely and important to take a critical look at what evidence actually exists in support of the anti-epinephrine dogma preached by some, and what evidence supports the safety of its use by others.

METHODS

We performed an in-depth review of the literature surrounding this topic. We carefully examined each of the 48 cases of digital necrosis cases associated with local anesthesia that Denkler[5] found when he performed his exhaustive review of the literature from 1880 to 2000. We also reviewed some of the evidence around the basic science of epinephrine and procaine. We examined each of the articles that have addressed the issue of epinephrine safety in the hand and fingers.

RESULTS

Evidence against the Elective Use of Epinephrine in the Finger

An in-depth review of the literature from 1880 to 2005[5,6] revealed that there were 48 cases of digital infarction associated with local anesthesia. Of those 48 patients, 21 had epinephrine injected with the local anesthetic. All of the evidence against the use of epinephrine in the finger rests with those 21 cases.[7–23]

A close look at the 48 infarction cases shows that there were more cases of digital necrosis with local anesthesia that *did not* involve epinephrine (27 cases)[15,17,18,24–35] than there were that *did* involve epinephrine (21 cases). The fact that there were actually more cases of local anesthetic-related digital infarction in which epinephrine was not involved leads to the logical conclusion that epinephrine was not the only factor inducing digital necrosis in the time period before 1950 when 42 of these cases occurred.[7–18,20–31] (Only six of these cases occurred after 1950.[19,32–35]) Something other than epinephrine had to have killed those 27 non–epinephrine-injected fingers.

What was different before 1950 that may have killed fingers injected with local anesthetics? One definite difference is that before 1950, procaine was almost the only local anesthetic used from its introduction in 1905 as Novocaine (the "new caine"), the first widely usable synthetic local anesthetic agent, until it was replaced with lidocaine's introduction in 1948.[36]

As a result, almost all of the 48 cases of finger death associated with local anesthetics involved procaine. The unknown agents most likely involved procaine as well because of the time of their reporting (Table 1).

An important clue to the deaths of the fingers injected with procaine without epinephrine comes from a 1948 warning by the Food and Drug Administration[37] about a recall of toxic batches of procaine (Novocaine) manufactured by the Kendall Company in the United States. Tissue necrosis had been produced by acidic batches of procaine without epinephrine, one with a pH as low as 1. We found other reports of procaine with epinephrine tissue necrosis in "non–end artery" locations such as the upper lip, face, scalp, buttock, leg,[38] abdomen,[39,40] scrotum,[41] and patella.[42]

How could toxic acidic doses of widely available procaine with a pH as low as 1 have been injected before 1950? The reason is that expiry dates on injectable medicines were only mandated in the United States in 1978,[43] and local anesthetic agents did not have expiry dates on the bottles before 1950. An article published in 1950 by Uri and Adler[44] noted that solutions of procaine that had been sitting on the shelf for some time were often noted to have a yellowish tint. They tested these aged, colored batches of procaine solution and found them to be toxic in rabbits. They admitted that before their experiment, the need to avoid the use of discolored solutions of procaine was not clear. They concluded that discoloration of procaine solutions was indicative of increased toxicity and that these solutions should no longer be used.

Procaine is an amino ester of an aromatic acid that undergoes degradation by hydrolysis both in vivo and in vitro. One of the products of the hydrolysis of procaine is para-aminobenzoic acid. As procaine degrades, the concentration of para-aminobenzoic acid increases and the pH of the local

Table 1. Digital Infarction Cases with Local Anesthesia with and without Epinephrine

Type of Local Anesthetic Used	Digital Infarction Cases with Local Anesthesia with Epinephrine	Digital Infarction Cases with Local Anesthesia without Epinephrine
Procaine (Novocaine)	18[7–10,12–18,20–23]	13[17,18,26,28–30,33]
Unknown agent	1[19]	8[15,17,31–35]
Cocaine	2[11]	4[24,26,27]
Eucaine		1[25]
Water		1[26]
Lidocaine	0	0
Total	21	27

anesthetic solution becomes increasingly acidic.[45] The pH of procaine solutions ranges from 3 to 5.5.[46] Buchi and Horler,[47] followed by Terp,[45] found the maximum stability of procaine in solution to be at a pH of 3.6, well below the physiologic pH of 7.4. In an attempt to prepare a solution of procaine that would sting less and have a more rapid onset of action, three separate teams of chemists attempted to create a procaine solution at a pH of 7.[47–49] All three teams concluded that stable procaine solutions cannot be created at a pH above 6.

In 1948, Terp[45] demonstrated that the rate of hydrolysis of procaine increased 3.1 times for every 10°C temperature increase. Two texts from 1920[50] and 1934[51] make no mention of the necessity of storing procaine in a cooled environment to prevent degradation. It is likely that much of the procaine in use underwent degradation to increasingly acidic pH values because of prolonged exposure to room temperature, because air conditioning was not widely available before 1950.

The articles on procaine toxicity published between 1948 and 1950 likely did not receive much attention, because lidocaine was introduced in 1948. Lidocaine quickly replaced procaine as the anesthetic of choice because, in addition to being toxic, procaine had a lower potency, slower onset of action, and shorter duration of action than lidocaine.[36] Procaine problems quickly became a thing of the past. Procaine is now a restricted drug that is not for human use in most countries.

It is also worth mentioning that three of the 21 epinephrine infarction cases were complicated postoperatively by excessively hot soaks causing burns.[20–22] Also, at least three of the 21 adrenaline infarct cases[23,29] described evidence of bleeding or pink color in the finger at the end of the case, which would not be compatible with a vasoconstrictive digital infarction but would be compatible with an acidic toxic progressive necrosis type of infarction.

In addition, the era of the digital infarction cases before 1950 was also the time of reusable glass syringes and reusable metal needles, which were sometimes left acidic with the cleaning and sterilizing processes of the day. This acidity from cleaning processes was implicated as the cause of extensive tissue necrosis in the Woolley and Roe case of 1947.[52] To summarize the above historical findings, there is clear evidence that outdated procaine sitting on the shelf before 1950 (the days before expiry dates) became as highly acidic as a pH of 1. There is also clear evidence that such procaine was injected into patients and caused tissue necrosis all by itself without epinephrine. It is also clear that procaine with epinephrine caused tissue necrosis in non–end artery sites in those days as well. Because the 21 epinephrine digital infarction cases that generated the anti-epinephrine dogma were all injected with procaine or cocaine, the anti-epinephrine dogma evidence is not valid because epinephrine was injected with potentially toxic substances in every case.

Evidence for Elective Epinephrine Use in the Hand and Finger

Two separate in-depth reviews of the world literature,[5,6] and our own review, were not able to find one case of digital infarction associated with lidocaine with epinephrine.

Perhaps the most compelling argument for the safety of epinephrine in the finger is the introduction of phentolamine, the epinephrine vasoconstriction antagonist. Phentolamine is an alpha-blocker that was first reported in humans for this purpose in 1957.[53] There have been several reports of successful phentolamine reversal of high-dose (1:1000) epinephrine-induced vasoconstriction in the fingers.[54–66] This is 100 times the dose that is used clinically in elective epinephrine injection with local anesthesia (1:100,000). One of those high-dose epinephrine digits was salvaged with phentolamine 13 hours after injury.[57]

In a prospective, blinded, controlled study, Nodwell and Lalonde[67] showed that phentolamine (1 mg in 1 ml) injection in the same space as the epinephrine injection effectively, reliably, and completely reverses 1:100,000 epinephrine-induced vasoconstriction color changes in the finger in an average of 1 hour and 25 minutes. They also showed that it takes an average of 6 hours and 20 minutes for fingers to return to a normal color after the blanching effect of three injections of 2 ml each of lidocaine 2% with 1:100,000 epinephrine in the base of the proximal phalanx, in the base of the middle phalanx, and at the distal palmar crease. This time frame is well within the accepted limit of ischemia for fingers that has been established in digital replantation.

It is important to note that there is not one case of low-dose epinephrine digital infarction in the world literature (total number of such cases, 21) in which there was an attempt to use phentolamine to reverse the epinephrine vasoconstriction effect.[7–23] The cases of digital infarction associated with epinephrine before 1950 occurred years before the introduction of phentolamine in 1957.[53]

Concluding that epinephrine should be banned for its vasoconstrictive effect in the finger on the basis of cases in which the use of phentolamine rescue was not even considered is as invalid as concluding that morphine should never be used because of cases of lethal respiratory depression in which the use of naloxone antagonist was not even considered (Fig. 1). The use of phentolamine to reverse epinephrine vasoconstriction was not considered in any of the 21 epinephrine digital infarction cases that generated the anti-epinephrine dogma. This is the second reason that the anti-epinephrine dogma evidence is not valid.

In our own experience, the senior authors (D.H.L., K.A.D.) of this article participated in a prospective study in six cities with nine surgeons in which a total of 3110 consecutive low-dose (1:100,000) epinephrine injection cases were treated with 1340 injections into the fingers and 1770 injections into the hand. There were no cases of digital infarction, and phentolamine rescue was never required.[68] In addition, we know Canadian and American hand surgeons who have regularly injected low-dose epinephrine (1:100,000) with lidocaine into the finger and hand for a total of more than 300 surgeon years without a single case of infarction, and without a single case requiring the use of phentolamine rescue.

Furthermore, many other surgeons have reported the use of epinephrine for digital and hand surgery without any untoward effects.[69–72] In 1958, Burnham[73] reported on the use of lidocaine with 1:200,000 epinephrine in 93 digital blocks without complications. In 1979, McGlamry[74] recommended injecting lidocaine with epinephrine 1:100,000 for digital blocks. In 1985, Earle and Blanchard[75] used lidocaine with epinephrine for finger blocks at the level of the metacarpals. Johnson[76] reported 421 hand surgeries, of which 98 were digital, using lidocaine with epinephrine, with no ischemic complications. Steinberg and Block[77] reported more than 200,000 injections of lidocaine with epinephrine (1:100,000) in the foot, forefoot, and toes with no case of gangrene. Sylaidis and Logan[78] injected 100 consecutive fingers with relatively high concentrations of epinephrine (1:80,000) without any cases of digital gangrene. In 1998, Wilhelmi et al.[69] prospectively used epinephrine in 23 digital operations with no complications.

$$\frac{\text{Morphine}}{\text{Naloxone}} = \frac{\text{Epinephrine}}{\text{Phentolamine}}$$

Fig. 1. Analogy of the relationship of four drugs.

Physiology of Epinephrine and Skin Blood Flow

Epinephrine in the plasma is rapidly broken down by catecholamine *O*-methyl transferase and monoamine oxidase.[79] Its half-life in plasma is only 1.7 minutes.[80] In the skin blood vessels of the dog at rest, approximately 70 percent of cutaneous blood flow is shunt flow and only 30 percent of the blood flow is exchange (nutrient) blood flow. Local infusion of norepinephrine redistributes cutaneous blood flow so that 90 percent of the blood flow becomes exchange blood flow, and only 10 percent of blood flow is now shunt blood flow.[81] In other words, catecholamines preferentially vasoconstrict shunt blood flow in the skin, whereas they vasoconstrict nutrient circulation to a much lesser degree. Altinyazar and colleagues[82] provided evidence that epinephrine-injected fingers are in a low-flow state, not a no-flow state. These facts may help to explain why skin tolerates epinephrine vasoconstriction.

Implications for the Future of Hand Surgery

Adrenaline in elective hand and finger surgery means the deletion of the tourniquet for many operations, and therefore the deletion of sedation and general anesthesia and the need to perform these operations in the main operating room. This will have a profound effect on the practice of hand surgery and on how hospitals and payers will view hand surgery in the future.

It is difficult to tell where the pendulum will settle on which cases will require an anesthesiologist and the main operating room and which will not. Certainly, complex mutilating hand injuries, cases with a lot of scarring such as recurrent Dupuytren's, and other difficult dissection cases will likely continue to be performed under general anesthesia for the foreseeable future. Also, many surgeons will be reluctant or unable to give up the totally bloodless field of the tourniquet, because adrenaline surgery is certainly not bloodless surgery.

On the other hand, many surgeons will not want to subject patients to the unnecessary risks of general anesthesia when they can perform some simple hand operations, such as carpal tunnel release, flexor tendon repair, operative reduction of finger fractures, and simple Dupuytren's contracture, under tourniquet-free pure local anesthesia with epinephrine. In addition, the conveniences

and reduced costs of performing hand surgery outside of the operating room under pure local anesthesia will also have a significant appeal for many surgeons.

In our own practices, we have found that having a wide-awake patient who is pain free and tourniquet free provides several advantages to operations such as flexor tendon repair. After the tendon is repaired, the patient can actively flex and gapping can be observed and corrected before the skin is closed. If unnecessary pulleys are impeding full active movement, they also can be divided before the skin is closed. The patient becomes a much better integrated partner in postoperative care after seeing his or her own tendon repaired and receives uninterrupted education time from the surgeon during the procedure. The patient never jerks on the freshly repaired tendon as he or she awakes from general anesthesia. Similar advantages are observed in tendon transfers, such as extensor indicis proprius to extensor pollicis, during which the awake patient can compare flexion and extension in the two thumbs before the skin is closed to make sure transfer tension is correct. The patient who has undergone Dupuytren's contracture not only has avoided general anesthesia but also has seen a new range of pain-free motion that can be worked toward postoperatively. The patient undergoing tenolysis can comfortably pull on his or her own tendon to help the surgeon release it without experiencing the pain or rush induced by tourniquet time. The patient undergoing joint fusion can confirm joint fusion position by moving the hand with temporary Kirschner wires before final fusion is accomplished and the skin is closed. Patients undergoing arthroplasty can actively move their fingers to make sure the extensors are properly adjusted before the skin is closed.

In our own practices, we do not inject epinephrine in patients who have evidence of severe preoperative ischemia, such as ischemic finger tips due to diseases such as scleroderma or Raynaud's. We do not inject previously replanted digits or anyone whose finger circulation seems doubtful. However, contraindications to epinephrine in the finger are still not well established. We suspect that the circulation will have to be assessed by the surgeon in each case, just as is done before injection of epinephrine in the nose or the ear.

With the hundreds of thousands of digital blocks performed around the world daily, it is inevitable that someday someone will inject a barely viable finger with epinephrine, not know about phentolamine rescue, and cause a digital infarction. Surgeons will have to exercise care and report adverse events should they occur so that contraindications to epinephrine injection in the fingers can become well established, just as adverse events and contraindications to general anesthesia are reported and established.

CONCLUSIONS

The pre-1950 case reports that created the evidence generating the dogma that epinephrine should never be used in the finger are not valid evidence for the following reasons: (1) The cases were also associated with procaine or cocaine injection, which were clearly shown to be potentially toxic in their own right, and (2) none of those cases considered the use of phentolamine rescue because this drug was introduced in the time period after the pre-1950 case reports. On the other hand, the clinical evidence contradicting the dogma that epinephrine should never be used in the finger is compelling. However, just as morphine must be used in judicious doses and only with the knowledge of naloxone rescue, surgeons who use low-dose (1:100,000) epinephrine electively should understand how to use phentolamine and be able to rescue epinephrine vasoconstriction with phentolamine in the finger if it should be required. Because contraindications to epinephrine injection in the finger are not well established, it should likely continue to be used with caution in poorly vascularized fingers. With these caveats in mind, it is time that textbooks stating that epinephrine should not be injected in the fingers be revised in future editions.

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DISCLOSURES

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