The Anesthetic Effects of Lidocaine with Epinephrine in Digital Nerve Blocks

A Systematic Review

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There is a long-standing stigma associated with the use of epinephrine in digital nerve blocks (DNBs) over the concern of digital necrosis. We conducted a systematic review to assess the duration of anesthesia, onset of anesthesia, and complications of lidocaine with epinephrine compared with plain lidocaine for DNBs in adults. We searched Medline via Ovid, Cochrane Library, and ClinicalTrials.gov on January 28, 2020. We included randomized controlled trials that examined lidocaine with epinephrine 1:80,000 to 1:1,000,000 (1–12.5 μg/mL) and plain lidocaine for DNBs of fingers or toes in adults. We completed a blinded review of all unique articles, followed by full-text reviews, data extraction, and quality assessment of all eligible trials. Risk of bias was assessed to inform qualitative data analysis. We identified seven studies with a combined 363 adults and 442 DNBs that met the inclusion criteria. All five studies that reported duration of anesthesia established longer duration in the epinephrine-supplemented lidocaine group, with significant increases in three. Two of the three studies that reported the onset of anesthesia demonstrated significant differences. The two studies that reported complications did not have a single case of digital necrosis. In adults, the use of lidocaine with epinephrine 1:80,000 to 1:1,000,000 (1–12.5 μg/mL) for DNB yields a longer duration of anesthetic effect and seems to be as safe as plain lidocaine in healthy adults. Several studies had some concern for bias, and additional studies are warranted. (J Am Podiatr Med Assoc 113(4), 2023)

Poorly managed acute postoperative pain is associated with quality-of-life impairment, delayed recovery time, higher health-care costs, and prolonged duration of opioid use.[1] In patients undergoing digital surgery, digital nerve blocks (DNBs) with plain lidocaine are commonly used to eliminate perioperative pain and reduce postoperative pain by a variety of physicians and surgeons, including dermatologists, emergency physicians, plastic surgeons, orthopedic surgeons, podiatric physicians, and foot and ankle surgeons.[2,3] The impact of local anesthetics on postoperative pain reduction largely depends on the duration of the anesthesia.[1] Epinephrine, a common vasoconstrictor, serves to reduce or slow the diffusion of the anesthetic outside of the injected area, which prolongs the duration of their effects; in application, epinephrine has been observed to increase the duration of lidocaine in a variety of nerve blocks.[4]

There is a long-standing stigma associated with the use of epinephrine in DNB due to a concern over the possibility of digital necrosis secondary to vascular insufficiency, with the rationale that epinephrine causes vasoconstriction via α-receptions in the terminal arteries of digits.[5-7] Although the early concerns came in previous decades, in 1944 Bunnell recommended against the use of epinephrine in the

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digits of the upper extremity in his comprehensive textbook *Surgery of the Hand*.[8,9] In 1971, Steinberg and Block[10] demonstrated the safe use of lidocaine with epinephrine in more than 200,000 various injections and blocks of the foot, forefoot, and toes; however, their findings were criticized by those who repeatedly claimed that epinephrine is unsafe for DNBs.[7] Disagreement on the topic created a lack of consensus around the efficacy and safety of epinephrine supplementation for DNB and has resulted in an avoidance of local anesthetic–epinephrine combination solutions, such as lidocaine with epinephrine, that has been declining but still persists to this day.[11]

To familiarize podiatric physicians with the efficacy of lidocaine with epinephrine in DNBs in adult patients, we conducted a systematic review of the anesthetic effects—duration of anesthesia, onset of anesthesia, and complications—of lidocaine with epinephrine compared with plain lidocaine for DNBs in adult patients. In 2015, Prabhakar et al[11] conducted a systematic review with somewhat similar outcomes; however, only four studies fit their inclusion criteria and only one contained their primary outcome.

Methods

Review Protocol

We used a standard protocol to identify relevant studies for this review. Analysis was conducted according to the *Cochrane Handbook for Systematic Reviews of Interventions* guidelines and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist to report methods and findings.[12,13] The original protocol is available on request; a record of changes made after initiation of the review is outlined in Appendix 1.

Study Eligibility Criteria

We included randomized controlled trials (RCTs) that examined the use of lidocaine with epinephrine for DNBs compared with lidocaine alone in adult patients. We included all concentrations of lidocaine and all concentrations of epinephrine. The RCTs must have had an identical control plain lidocaine concentration. Furthermore, each RCT must have included duration of anesthesia measured in units of time as an outcome and included only adults, defined as individuals 18 years or older. Full inclusion criteria and justifications are listed in Appendix 2.

Outcome Measures

The primary outcome measure was the duration of anesthesia. All of the values were converted to hours. We chose this as the primary outcome because epinephrine is known to promote vasoconstriction, which when used in tandem with lidocaine, delays clearance of the anesthetic and thus extends the duration of anesthesia.[14] Duration of anesthesia was defined differently in each study but was collected as a single variable.

Secondary outcomes included mean onset of anesthesia and complications. Mean onset of anesthesia is fundamental to assess anesthetic efficacy and was defined as the time taken from injection of the anesthetic to onset of numbness in the anesthetized area. All onset of anesthesia values were converted to seconds. We recorded complications, including relative risk of digital necrosis or gangrene. If not provided, relative risk of digital necrosis or gangrene was calculated as the number of participants who developed digital necrosis or gangrene divided by all of the participants given anesthetic. Injuries such as these are a major component of clinician reluctance to use epinephrine in digital blocks.[14]

Search Methods

We searched MEDLINE, SCOPUS, and the Cochrane Library (each from its origin to January 28, 2020) with the help of a research librarian to identify articles for inclusion. We used both keywords and MeSH terms related to the themes of lidocaine with epinephrine, nerve blocks, and digits in the searches. Results from each of these themes were combined with "AND" to ensure relevancy in the final search results. No limits were added to the search. To identify additional articles, we reviewed the reference lists of included studies. Search strategies for each source are listed in Appendix 3.

Study Selection

Two blinded reviewers (Brandon M.B. [subsequently B.M.B.], J.K.M.), including one content expert (B.M.B.), reviewed the titles and abstracts of all potential studies to assess adherence to the inclusion criteria. A third reviewer (A.S.A.) was available to resolve conflicts via discussion. The two reviewers (B.M.B., J.K.M.), independently and in duplicate, assessed the full text of articles determined to be relevant in the title and abstract review. If any disagreements had arisen, they would have been resolved by discussion at each step by a third reviewer (A.S.A.).

Data Collection

Two nonblinded, independent reviewers (B.M.B., A.S.A.) extracted data in duplicate from studies that met the inclusion criteria using a piloted, standardized data collection form. Units were converted to ensure continuity within variables. Disagreements were resolved via discussion. The following information was extracted from each paper if available: publication data, methods, and results, including duration of anesthesia, mean onset of anesthesia, and complications. The data collection form is outlined in Appendix 4.

Assessment of Methodological Quality

Given that this review included only RCTs, we used the six-item risk of bias tool to assess the risk of bias for each study.[15] Two independent, nonblinded reviewers (A.S.A., J.K.M.) conducted this assessment. Disagreements were resolved via discussion. Information from the risk of bias tool informed assessment for need and completion of both sensitivity and subgroup analyses.

Analysis

Measure of Treatment Effect. We assessed the mean difference and standard deviation between the intervention and control groups for all relevant outcomes. Complications were assessed via relative risk. Qualitative differences between the groups per variable were then assessed for statistical significance.

Management of Missing Data. We excluded any study that lacked data pertaining to a primary or secondary outcome from qualitative analysis.

Data Synthesis. All data for each outcome provided in each paper was recorded in the data collection form (Appendix 4). Duration of anesthesia data were converted to hours, and onset of anesthesia was converted to seconds. Qualitative summarization was then conducted by assessing the proportion of studies with statistically significant differences, the direction of the relationship between the intervention and the outcome per study, and the sample size per study. We intended to assess results via meta-analysis if enough data were reported.

Assessment of Heterogeneity. We assessed heterogeneity by sequentially comparing the statistical significance, direction of the relationship, sample size, and then measurement method for each study compared with the others.

Assessment of Reporting Biases. We intended to assess publication bias via generation of a funnel plot to plot studies by finding regarding duration of anesthesia and study size. However, we elected not to do this because of the smaller number of studies included in the review.

Sensitivity Analyses

We identified differing sample size as a source of heterogeneity in the included studies. Results were qualitatively assessed by sample size.

Results

Description of Studies

Results of Search. We found 1,667 studies through a search strategy of Medline via Ovid, SCOPUS, Cochrane Library, and Clinicaltrials.gov. Of the initial 1,667 articles, we removed 767 duplicates and found 900 unique records. We scanned only 880 of the 900 unique articles for inclusion because 20 studies were ongoing. Of the 880 articles that were screened for eligibility, we excluded 869 by abstract and title review. We assessed 11 articles for eligibility through full-text review and excluded four due to inappropriate study design. Ultimately, seven trials were included (Fig. 1).

Included Studies. Seven trials were included for final review.[6,16-21] These studies included 442 DNBs and 363 participants. Mean patient age ranged from approximately 25 to 44 years. Most studies included mostly men. Type of procedure and digit varied by study. Of the seven articles, five reported duration of anesthesia,[16,17,19-21] three reported time taken to onset of anesthesia,[18,20,21] and two reported complications.[6,17] Of those, three reported significant mean differences in duration of anesthesia,[17,19,21] two reported significant differences in onset of anesthesia,[18,20] and none reported worse complications with epinephrine.[6,17] Three of the studies had smaller sample sizes of 12 to 30 participants,[16,19,20] three studies had medium sample sizes of 43 to 60 participants,[6,17,18] and one study had a large sample size of 86 participants (Table 1).[21]

Methodological Quality of Included Studies

Five of the seven included studies had somewhat concerning risk of bias overall,[6,16,18-20] and the other two had high risk of bias (Fig. 2).[17,21] In particular, both Andrades et al[17] and Mohd Rashid et al[21] had questionable outcome measurement methods that introduced high risk of bias; the former relied on participants to recall duration of

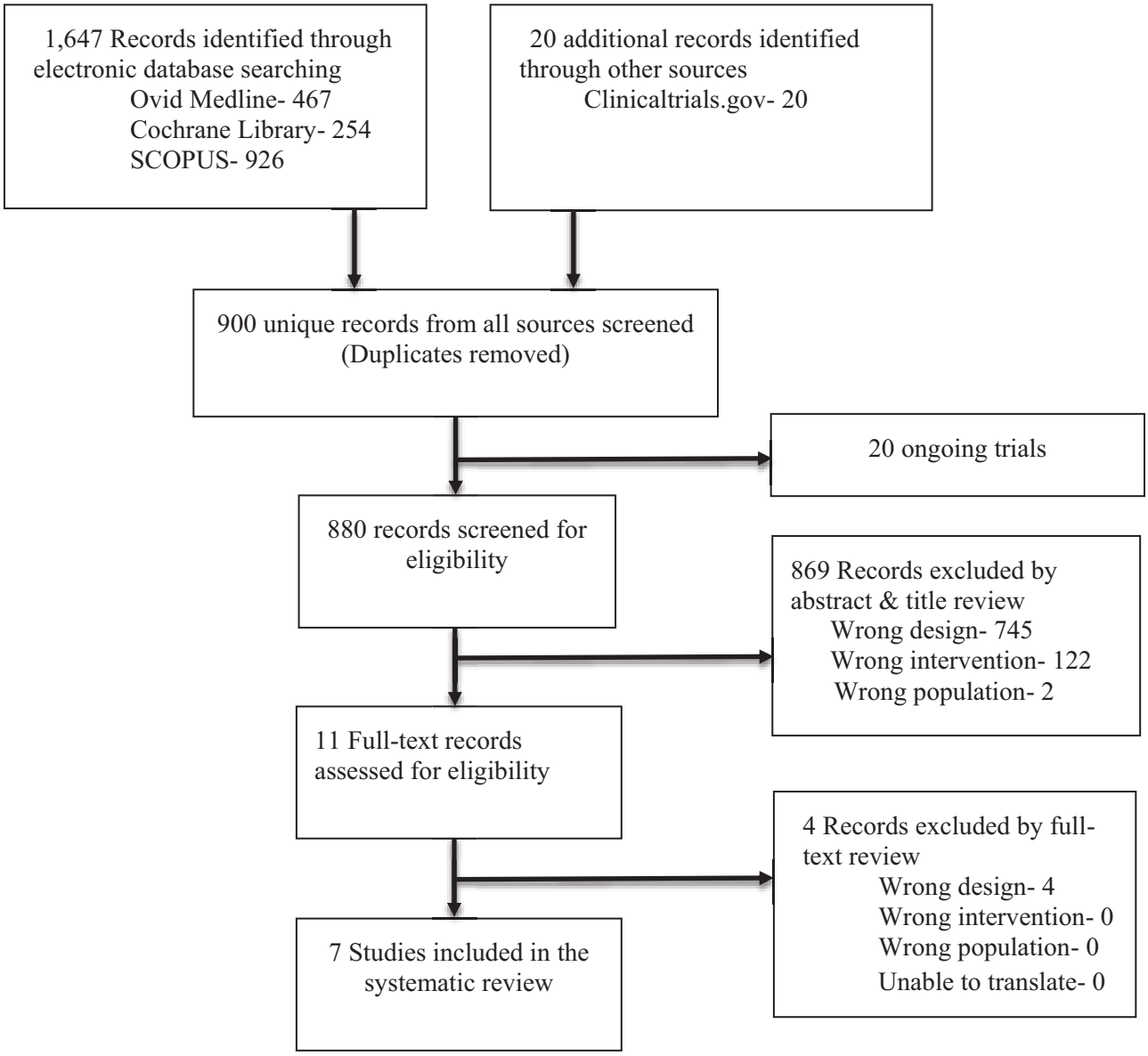

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study selection flow diagram.

anesthesia, but no additional guidelines were reported to have been given to participants for this purpose. Parties responsible for assessing onset of anesthesia in the latter were aware of participant assignment, and the method of assessing onset of anesthesia was subjectively defined.[17] Andrades et al[17] also did not report whether participants were blinded to assignment, and the party responsible for assessing outcomes was unclear, introducing high risk of bias. All of the included studies had some concern of bias in that it was not clear whether an analytic plan was established a priori and followed.

Effects of Intervention

Duration of Anesthesia. Of the seven included studies, five reported duration of anesthesia[16,17,19-21]; only three of those presented a *P* value. Thomson and Lalonde[16] reported a higher duration of anesthesia in the intervention group (mean difference, 5.5 hours; 110%; *P* value not given), as did Prasetyono and Lestari[20] (mean difference, 1.45 hours; 87.3%; *P* value not given), but significance was not mentioned (Table 2). Significantly longer duration of anesthesia with epinephrine[17,19] was reported by Sönmez et al[19] (mean difference, 3.3 hours; 69%; $P < .001$), Andrades

Table 1. Characteristics of Included Studies

Study and Year	Blocks (No.)	Participants (No.)	Sample Size Group	Participant Age (mean ± SD [years])	Male Sex (%)	Significant Difference at Baseline	Type of Procedure	Type of Digit	Intervention Dose	Comparison Dose
Thomson and Lalonde,[16] 2006	90	30	Small	NP	NP	NP	Single volar injection at the metacarpophalangeal flexion crease	Right and left long finger; either left or right small finger	2% Lidocaine with epinephrine 1:100,000	2% Lidocaine
Prasetyono and Lestari,[20] 2016	24	12	Small	27	100	None	Injection	Ring fingers	0.2% Lidocaine with epinephrine 1:1,000,000	2% Lidocaine
Córdoba-Fernández et al,[18] 2019	56	56	Medium	Control: 24.46 ± 6.29 Intervention: 24.57 ± 6.94	50	None	Injection with "inverse V" dorsal approach	Selected second toe	2% Lidocaine with epinephrine 1:100,000	2% Lidocaine
Wilhelmi et al,[6] 2001	60	60	Medium	NP	NP	NP	Post-traumatic injuries or elective conditions	Varied	1% Lidocaine with epinephrine 1:200,000	1% Lidocaine
Sönmez et al,[19] 2008	20	20	Small	Control: 44 ± 18 Intervention: 36 ± 12	80	None	Varied	Varied	2% Lidocaine with epinephrine 1:80,000	2% Lidocaine
Andrades et al,[17] 2003	50	43	Medium	Control: 32.4 Intervention: 32.3	Control: 82 Experiment: 71		Varied	Fingers or toes	2% Lidocaine with epinephrine 1:100,000	2% Lidocaine
Mohd Rashid et al,[21] 2019	86	86	Large	NP	31	None	Trigger finger for 37% of intervention group; ring finger for 30% of control group	Index, ring, middle, thumb, and little finger	1% Lidocaine with epinephrine 1:100,000 and 1 mL of 8.4% sodium bicarbonate	1% Lidocaine with 1 mL of sodium bicarbonate

Abbreviation: NP, not provided.

Figure 2. Risk of bias.

et al[17] (mean difference, 2.2 hours; 92%; $P < .05$), and Mohd Rashid et al[21] (mean difference, 2.77 hours; 67.7%; $P < .001$).

Onset of Anesthesia. Three of seven studies reported onset of anesthesia.[18,20,21] Prasetyono and Lestari[20] and Córdoba-Fernández et al[18] reported significant results at the 95% confidence level, but Prasetyono and Lestari reported delayed onset of anesthesia (mean difference, 240 sec; 400%; $P = .04$),[20] whereas Córdoba-Fernández et al[18] reported earlier onset of anesthesia (mean difference, –41 sec; –30%; $P < .001$) (Table 3). Mohd Rashid et al[21] also reported earlier onset of anesthesia, but the result was not significant (mean difference, –17 sec; –16.6%; $P = .204$).

Complications. Two of the seven studies reported complications (Table 4).[6,17] Wilhelmi et al[6] reported a greater risk of complication without epinephrine but did not report a P value (complication prevalence, 6.9%). Andrades et al[17] reported an approximately 4% lower risk of complications with epinephrine use, although no P value was given

Table 2. Duration of Anesthesia

Study and Year	Participants, Intervention/ Control (No.)	Duration of Anesthesia (Mean [95% CI] [h])		% Change with Epinephrine	*P* Value
		Epinephrine with Lidocaine	Lidocaine Plain		
Thomson and Lalonde,[16] 2006	30/30	10.4 (9.4–11.4)	4.9 (4.2–5.6)	110	NR
Prasetyono and Lestari,[20] 2016	12/12	3.11 (1.68–4.55)	1.66 (0.64–2.68)	87.3	NR
Córdoba-Fernández et al,[18] 2019	28/28	NR	NR	NA	NR
Wilhelmi et al,[6] 2001	31/29	NR	NR	NA	NR
Sönmez et al,[19] 2008	10/10	8.1 (6.14–9.7)	4.8 (3.62–6.0)	69	<.001
Andrades et al,[17] 2003	21/22	4.6	2.4	92	<.05
Mohd Rashid et al,[21] 2019	43/43	6.86 (3.98–9.74)	4.09 (1.80–6.38)	67.7	<.001

Abbreviation: NA, not applicable; NR, not reported.

Table 3. Onset of Anesthesia in Seconds

Study and Year	Participants, Intervention/ Control (No.)	Onset of Anesthesia (Mean [95% CI] [sec])		% Change with Epinephrine	*P* Value
		Epinephrine with Lidocaine	Lidocaine Plain		
Thomson and Lalonde,[16] 2006	30/30	NR	NR	NA	NR
Prasetyono and Lestari,[20] 2016	12/12	300 (60–540)[a]	60 (60–360)[a]	400	.04
Córdoba-Fernández et al,[18] 2019	28/28	94 (44.8–143.2)	135 (211.5–58.5)	–30	<.001
Wilhelmi et al,[6] 2001	31/29	NR	NR	–	NR
Sönmez et al,[19] 2008	10/10	NR	NR	–	NR
Andrades et al,[17] 2003	21/22	NR	NR	–	NR
Mohd Rashid et al,[21] 2019	43/43	85.16 (0–201.2)	102.07 (123.32–225.39)	–16.57	.204

[a]Median (range).
Abbreviations: NR, not reported.

(relative risk, 0.79). Neither study reported an incidence of digital necrosis.

Heterogeneity. Although there was no marked heterogeneity in duration of anesthesia, which was reported by all included studies as being longer with epinephrine use, or complications, which were reported to be less frequent with epinephrine use, onset of anesthesia results were heterogeneous. Given the differences in type of nerve block, amount of anesthetic used, and procedure performed across studies, we did not develop summary estimates for the outcomes.

Sensitivity Analyses. We identified three approximate groupings of study sample sizes: Prasetyono and Lestari,[20] Sönmez et al,[19] and Thomson and Lalonde[16] with small sample sizes; Andrades et al,[17] Wilhelmi et al,[6] and Córdoba-Fernández et al[18] with medium sample sizes; and Mohd Rashid et al[21] with a large sample size. In the small sample size group, only significant *P* values were reported.[16,19,20] The medium sample size group reported *P* values in a greater proportion of cases than did the small size group.[6,17,18] The larger sample size study, Mohd Rashid et al,[21] reported both a significant and a nonsignificant result. Qualitatively, the results of the mid-sized studies tended to be more significant, but with so few included studies, this assessment is not reliable.

Subgroup Analyses. No subgroup analyses were performed.

Publication Bias. Too few studies fit within the inclusion criteria to assess for publication bias for any of the outcomes. Mohd Rashid et al[21] reported nonsignificant findings for onset of anesthesia, and Wilhelmi et al[6] did not report significance for complications, suggesting that there may be some publication bias but that it is not pervasive.

Discussion

The present analysis of duration of anesthesia including data from more than 200 patients clearly and homogeneously indicates that the use of epinephrine with lidocaine prolongs duration of anesthesia. Evidence regarding the impact of epinephrine supplementation on onset of anesthesia and complications is less robust. The claim that epinephrine with lidocaine hastens onset of anesthesia may be

Table 4. Risk of Complications

Study and Year	Participants, Intervention/ Control (No.)	Risk of Complications (%)		Relative Risk	*P* Value
		Epinephrine with Lidocaine	Lidocaine Plain		
Thomson and Lalonde,[16] 2006	30/30	NR	NR	–	NR
Prasetyono and Lestari,[20] 2016	12/12	NR	NR	–	NR
Córdoba-Fernández et al,[18] 2019	28/28	NR	NR	–	NR
Wilhelmi et al,[6] 2001	31/29	0	6.90	0	NR
Sönmez et al,[19] 2008	10/10	NR	NR	–	NR
Andrades et al,[17] 2003	21/22	14	18	0.79	"Significant"
Mohd Rashid et al,[21] 2019	43/43	NR	NR	–	NR

NR, not reported.

clinically useful despite the need for further confirmation. There is insufficient evidence to comment on the risk of complication with epinephrine supplementation in all patient populations, such as those with peripheral vascular disease.

Neither Prasetyono and Lestari[20] nor Thomson and Lalonde[16] reported a significant difference in duration of anesthesia, but the intervention and control groups included only 12 participants each in the former study. Thomson and Lalonde[16] reported duration of anesthesia values that were significant despite lack of mention as such ($P < .05$). Epinephrine with lidocaine was reported to both significantly hasten and prolong onset of anesthesia as per Córdoba-Fernández et al[18] and Prasetyono and Lestari,[20] respectively, but, again, Prasetyono and Lestari presented the delay with only 12 participants per group; the shorter time reported by Córdoba-Fernández et al[18] is more believable due to the larger sample sizes. In addition, Prasetyono and Lestari may have had methodological flaws that contributed to biased outcome measurement; sensation was checked at 5-min increments to assess onset of anesthesia, which likely exaggerated results.[18,20] Mohd Rashid et al,[21] with a sample size of 43 individuals per group, reported a greater, although nonsignificant, delay with plain lidocaine. The relationship between epinephrine use and onset of anesthesia remains uncertain. The limited studies reporting complications also contributes to some uncertainty; however, no reports of digital necrosis were made, and the use of epinephrine never results in increased complications.[6,17] Wilhelmi et al[6] and Mohd Rashid et al,[21] the only two to report complication results, reported fewer complications with epinephrine supplementation, although the former made no assessment of significance and the latter reported nonsignificant results. Overall, 1% to 2% lidocaine with epinephrine 1:80,000 to 1:1,000,000 (1–12.5 μg/mL) seems to significantly prolong the duration of anesthesia, may contribute to a change in time taken to onset of anesthesia, and poses no increased risk of complications.

Limitations and Strengths. This review has several limitations. All of the included studies had at least some concern of bias. Two of the three studies reporting significantly longer duration of anesthesia had high risk of bias, but the other three studies reporting the same increase make this trend believable. Despite problems with bias introduced by outcome measurement in the studies by Andrades et al[17] and Mohd Rashid et al,[21] their methods across studies were similar enough to compare results qualitatively. We also only included trials with adults without regard for peripheral vascular disease. More trials involving patients who are realistic candidates for digital procedures, such as patients with a history of diabetes and microvascular disease, would be useful in further debunking the stigma surrounding the use of epinephrine in DNB. The removal of duplicate articles was performed using the Rayyan QCRI software by one of us (A.S.A.). To prevent evidence selection bias, Rayyan QCRI was then used for a blinded and independent review of all unique articles by two of us. There were no disagreements on excluded articles. The same two authors independently completed full-text reviews, data extraction, and quality assessment of all eligible trials. Once again, there were no disagreements.

These results represent an advancement from the most recent systematic review to assess possible benefits of epinephrine use with lidocaine; whereas Prabhakar et al[11] reported only duration of anesthesia from one trial and noted high risk of bias, we noted a conclusive increase in duration of anesthesia with epinephrine-supplemented lidocaine. In contrast to Prabhakar et al, we observed less risk of complication with lidocaine-supplemented epinephrine. In addition, mean onset of anesthesia has not yet been included in a systematic review of this sort.

Implications for Practice. The present analysis suggests that use of lidocaine with epinephrine 1:80,000 to 1:1,000,000 (1–12.5 μg/mL) can result in earlier onset time for anesthesia, yields hours more of anesthetic effect compared with plain lidocaine, and poses no increased risks of complications, including digital necrosis, in adults without peripheral vascular disease. Case reports of digital necrosis that have involved epinephrine injections intended for anaphylaxis can carry epinephrine concentrations of 1:1,000, which is 80 times more potent than the dose of 1:80,000; however, as with all drugs, quantity matters, and an accidental injection will not necessarily result in digital necrosis.[22,23] As with any intervention, the risks and benefits must be weighed against each other; clinicians should not automatically avoid using lidocaine with epinephrine for DNB in healthy adult patients. The enhanced duration of anesthetic effect could be beneficial for many patients undergoing digital surgery. Although the use of lidocaine with epinephrine 1:80,000 to 1:1,000,000 (1–12.5 μg/mL) in adults is as safe as plain lidocaine for DNB in healthy adults, there is limited evidence on the safety of lidocaine with epinephrine in patients with peripheral vascular disease. To further disprove the stigma associated with the use of epinephrine in DNB, more trials with

low risk of bias are needed to understand the impact of epinephrine-supplemented lidocaine on patients with peripheral vascular disease. However, one can argue that in patients with peripheral vascular disease, the use of epinephrine is not critical because these patients will likely have slower clearance of the anesthetic, such as plain lidocaine, due to the already altered vascularization. Furthermore, digital tourniquets seem to be more problematic than epinephrine.[24]

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APPENDIX

Appendix 1. Changes to Search Method

Date of Change	Change	Justification
1/14/2020	We dropped the English language as a limitation	The limitation was unnecessary
1/28/2020	We included *anesthesia* as a keyword	Addition of this keyword expanded our search results to include more pertinent articles

Appendix 2. Inclusion Criteria and Justifications

Category	Inclusion Criterion	Specifics	Justification	Order
Intervention	Lidocaine with epinephrine	All doses included	The inclusion of all doses and concentrations will provide a comprehensive answer to the research question	1
Control	Lidocaine alone	Lidocaine dose must be the same as the intervention group	This will isolate the effect of adding epinephrine	2
Outcome	Duration of anesthesia	Any unit of time	Seconds, minutes, and hours are interconvertible	3
Study design	RCT	RCTs only	RCTs offer the strongest evidence available and increased comparability.	4
Population	Adults	Participants must be ≥18 years old	Adults are the most relevant population with the greatest interest in this review	5

Abbreviation: RCT, randomized controlled trial.

Appendix 3. Search Strategies

Theme	MeSH terms (exploded)	Keywords
Lidocaine with epinephrine	*Lidocaine, Epinephrine*	*Adrenaline, epinephrine, lidocaine*
Nerve block	*Anesthesia, Local, Nerve Block*	*Local anesthesia, local block, local anesthetic, nerve block, anesthesia*
Digits	*Toes, Fingers*	*Digit, digital, toe, finger, hallux, thumb, phalange*

Medline via Ovid, Cochrane Library, and ClinicalTrials.gov were searched from inception to January 28, 2020.

Appendix 4.
Data Collection Form

We included the following variables:

Publication Information.

Reviewer initials, Study ID (Author, Year), Date of Extraction, Full Citation, Trial Registration #, Author, Year, Country, Setting, Funding Source

Methods.

Number of Subjects, Age of Subjects (mean, standard deviation), Percentage Male, Significant Dierences at Baseline, Baseline Diagnosis, Type of Procedure, Type of Digit, Intervention Dose, Comparison Dose, General Findings

Outcome Data.

For Duration of Anesthesia, Onset of Anesthesia, and Complications outcomes:

Subgroups, For intervention and control groups: Mean, Standard Deviation, Number of Participants; For comparison of groups: Mean dierence or other summary measure, 95% confidence interval, *P* value