Onset Time of Local Anesthesia After Single Injection in Toe Nerve Blocks: A Randomized Double-Blind Trial
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**Purpose:** The study was conducted to investigate the onset time and safety profile of four different local anesthetic solutions.

**Design:** Randomized controlled clinical trial study.

**Methods:** One hundred twelve healthy volunteers were assigned to receive digital block on their second toe. Individuals were randomly assigned to one of the following groups: lidocaine 2%, lidocaine 2% with epinephrine, bupivacaine 0.5%, or bupivacaine 0.5% with epinephrine. Onset time was measured until detecting the absence of pinprick sensation. Oxygen saturation was measured in the infiltrated toe up to 60 minutes.

**Findings:** The subjects in the groups of anesthetics with epinephrine had a significantly lower mean onset time. There were no significant differences regarding oxygen saturation between the groups and no adverse effects were recorded.

**Conclusions:** The use of anesthetics with epinephrine can be an effective form of local anesthetic for digital blocks when a rapid onset of action, prolonged duration of anesthesia, and vasoconstrictive action are required.

**Keywords:** local anesthesia, digital nerve block, onset time, epinephrine.

**DIGITAL NERVE BLOCK** (DNB) is shown to be an effective procedure in elective or traumatic foot and hand ambulatory surgery. Digital blocks are superior to local infiltration and usually require smaller doses of anesthetic, avoid physical distortion of the tissue to be treated, and reduce the risk of bleeding during surgery with addition of epinephrine to the anesthetic agent. Digital blocks are commonly performed in patients with injured digits where the use of a tourniquet is inappropriate, as in tendon repairs where active testing may be required. In certain settings, especially in emergency departments, it is beneficial for the anesthetic agent to have a rapid onset of action, vasoconstrictive properties, and adequate duration of anesthesia. All this allows the surgical procedure to start in a short period of time, be carried out without unnecessary haste, with little bleeding, and without the need for additional infiltrations. Prolonged duration of anesthesia after DNB may also present the advantage of reducing the patient’s requirement for continuing analgesics. The most frequently used anesthetics for DNB are lidocaine and bupivacaine, which are available
for use with or without epinephrine. The available evidence indicates that average onset time after DNB with lidocaine 1% is about half that achieved with bupivacaine 0.5% but with shortest mean duration of anesthesia.4 Existing studies seem to show that the addition of vasoconstrictor to the lidocaine solution reduces the time to onset anesthesia for DNB and increases the anesthetic effect almost twice as long.5,6 However, adding epinephrine to bupivacaine does not seem to add a clinically significant length of time to pain relief.7

For decades, the convenience of using local anesthetic solutions with vasoconstrictors in DNB has been questioned, and currently no concrete and definitive evidence of the absence of danger or significant advantages of this approach has been substantiated. However, a lack of reported complications suggests that the risk of epinephrine-induced vasoconstriction to digits may be overstated.8,9

Clinical trials that have clinically evaluated the onset time and the duration of anesthetic effect of different solutions with or without epinephrine in DNB show contradictory results and limited applicability to the current practice. The systematic reviews on this topic show that there is no consensus on which anesthetic agent is the most appropriate for DNB and conclude that more prospective studies are necessary that focus on outcomes such as onset time, adverse events, and duration of postoperative pain relief.10,11 On the other hand, no prospective study has previously analyzed the ability of epinephrine to accelerate anesthesia onset in DNB. We hypothesized that the presence of a vasoconstrictor increases the anesthetic effect, thus reducing the onset time. The primary outcome of this study was to evaluate the onset time of anesthesia among four groups of anesthetic solutions with or without epinephrine after DNB of the toes. Secondarily, the oxygen saturation (SO2) in the infiltrated toes was evaluated.

Methods

Study Design and Sitting

This was a prospective single-center, randomized, double-blind clinical trial study with four parallel groups. The study was conducted at Área Clínica de Podología of the Universidad de Sevilla between February 2016 and July 2017.

Sample and Data Collection

The sample size necessary to estimate the difference in regard to the main study variable (onset time) was calculated assuming an alpha error probability of 5% and a power of 95%. G*Power 3.1.9 software (free software, Kiel University, Germany, 2014) was used to estimate the sample size. Initially 123 healthy volunteers among students of the podiatry degree and patients from the Área Clínica de Podología were recruited. Eleven subjects were excluded for different reasons. Finally, 112 participants were randomly assigned to one of the four study groups using random number generation with a 1:1 allocation using only one random block (Random Allocation Software 1.0 (M. Saghaei, Isfahan University of Medical Sciences, Isfahan, Iran). The subjects were assigned to one of the groups to receive DNB with dorsal approach in the selected second toe using 2 mL of four different injectable solutions: 2% lidocaine (group lidocaine), 2% lidocaine with epinephrine 1:100,000 (group lidocaine with epinephrine), 0.5% bupivacaine (bupivacaine group), or 0.5% bupivacaine with epinephrine 1:200,000 (bupivacaine group with epinephrine). The staff member generating the randomization sequence was not involved in patient recruitment or local anesthetic infiltration (Figure 1).

An independent assistant who was not involved in the study design, data collection, or analysis prepared the colorless codes for anesthetic solutions in transparent syringes and gave the preparation to the principal investigator, who then infiltrated the subject and made the pin-prick test. The codes were kept confidential by the technician until completion of the study. The staff member, independent assistant, and technician were not the same person. The participant, the principal investigator, and the technician in charge of chronometer were blind to the type of local anesthesia.

Study Protocol

The inclusion criteria were adult subjects with American Society of Anesthesiologists physical
status I or II and normal ankle-brachial index (0.9 to 1.2). Patients with a history of sensitivity to local anesthesia, peripheral vascular disease, diabetes mellitus, Raynaud’s syndrome, systemic sclerosis, CREST syndrome or patients with any vasospastic disorder, cardiovascular diseases, or pregnancy were excluded.

The assistant took samples of each solution used during the preparation and with a calibrated pH meter (Crison 507, Barcelona, Spain) the pH of each of the anesthetic solutions used was measured. The procedure consisted of local anesthetic infiltration in the root of the selected second toe with “inverse V” single dorsal approach. Using a 2 mL syringe and 27G dorsal ½ inch needle, 2 mL of the corresponding anesthetic solution previously prepared by an assistant was administered by the blinded investigator. All DNBs were performed in a standard manner in a maximum time of 20 seconds. The assistant started the chronometer after administration and stopped it when the patient had no pain after a pin-prick test under the nail matrix of the toe chosen. We used Neuropen (Owen Mumford), which is a pocket-sized device designed to provide a safe and reliable test that features a calibrated spring mechanism to deliver a 40 g sharpness test using Neurotips single use neurologic examination pins to assess reduced sensation to sharpness or pain in small nerve fibers. After anesthetic infiltration with 10-second intervals, the test was performed until the participant had no pain manifestation. This test is normally used to test pain for screening diabetic peripheral neuropathy and has been used in several studies to determine onset time after local anesthesia.5

Oxygen saturation (SO2) was measured in the infiltrated toe with a blood oxygen monitor NPB-40 (Covidien Spain Co, Ltd, Spain) and compared among groups. SO2 was measured at 1, 3, 5, 10, 20, 30, and 60 minutes after anesthetic administration. The appearance of adverse effects was assessed for 60 minutes and was collected by an assistant on an individual control chart. We considered a DNB infiltration safe when the SO2 was over 90%.

**Ethical Consideration**

This study was approved by Andalusian Biomedical Investigation Ethical Committee and was retrospectively registered to patient enrollment at ACTRN12616001610426. After information was

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Figure 1. CONSORT flow diagram. This figure is available in color online at www.jopan.org.
given, written informed consent was obtained from all participants in keeping with the principles of the Declaration of Helsinki and monitored by the Good Clinical Practice Unit at the Universidad de Sevilla Hospitals (Sevilla, Spain).

Statistical Analysis
Statistical analyses were performed using SPSS statistics software (version 24; IBM Corporation Inc, Chicago IL). The Shapiro-Wilk test showed that the data were normally distributed. The primary outcome measure (onset time) was assessed using the difference in the mean value and confidence intervals between the four groups. To analyze the results of this variable, a contingency table and analysis of variance (ANOVA) test for four groups were used. To corroborate whether there were statistically significant differences between the local anesthetics with or without epinephrine, Student’s t test was used. The secondary outcome measure (SO2) was assessed with ANOVA test, comparing the mean of the four groups in nine control points (preinjection, 30 seconds, 1, 3, 5, 10, 20, 30, and 60 minutes); likewise, we compared the differences between genders to determine statistically significant differences. \( P < .05 \) was considered statistically significant.

Results
From February 23, 2016 to July 7, 2017 a total of 123 subjects were recruited and randomly allocated to each one of the four equal study groups. Among these, eight subjects were excluded because they did not meet the inclusion criteria, and three subjects because of screen-failure. Likewise 27 subjects declined to participate in the study. Ultimately, a total of 112 participants were included, 28 in each group; all subjects completed the process according to the research protocol (Figure 1). The demographic characteristics and distribution of the study population are summarized in Table 1. There were statistically significant differences in onset time of anesthesia between study groups. The analysis showed that the onset time of anesthesia in the local anesthetics with epinephrine was shorter than that of the local anesthetics without epinephrine with significant differences (Table 2). There were no statistically significant differences in onset time in terms of gender.

With a confidence interval of 95%, we can affirm that the distribution of the variable (SO2) is the same for both categories \( (P = .126) \). The ANOVA test was not significant for any of the control tests (Table 3). There were significant differences in SO2 in the two groups with epinephrine in terms of gender at 5 and 10 minutes \( (P = .021) \). In the male group, SO2 remained stable during the study among the four groups (Figure 2); however, in two female epinephrine groups, SO2 descended to 94% 10 minutes after the injection and a punctual decrease took place at 20 minutes after the injection \( (P = .039 \text{ for lidocaine 2% with epinephrine group and } P = .001 \text{ for bupivacaine 0.5% with epinephrine group}) \) (Tables 4 and 5). No adverse

| Table 1. Baseline Demographic and Clinical Subjects Characteristics |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patients        | Lidocaine 2% Group | Lidocaine 2% With Adrenaline Group | Bupivacaine 0.5% Group | Bupivacaine 0.5% With Adrenaline Group |
| Male            | 28 (25%)         | 28 (25%)        | 28 (25%)        | 28 (25%)        |
| Female          | 14               | 14              | 14              | 14              |
| Age             | 24.46 ± 6.29     | 24.57 ± 6.94    | 25.54 ± 9.11    | 23.11 ± 4.22    |
| Ankle-brachial index | 1.014         | 1.023           | 1.017           | 1.051           |
| Temperature anesthetic (°C) | 26 ± 0.3      | 26.1 ± 0.2      | 25.8 ± 0.2      | 26.2 ± 0.1      |
| pH              | 6.1 ± 0.3        | 4.4 ± 0.7       | 6.0 ± 0.4       | 4.5 ± 0.8       |

Values are represented as the mean ± SD, number of patients n (%), or median (interquartile range).
effects were recorded in any of the groups in our study.

Discussion

Currently, several local anesthetic options are available for DNB; however, little consensus exists as to which agent is most appropriate. The available evidence indicates that addition of epinephrine to lidocaine provides good long-term anesthesia and may reduce the need for postoperative analgesia.6,10,11 No prospective study has analyzed as the main aim the ability of the vasoconstrictor to accelerate anesthesia onset in DNB. The results of the present study show that the addition of epinephrine significantly reduces the onset time of the anesthetic solution used. Significant differences were found between all four groups for the main variable, with shorter onset time in anesthetic solutions with vasoconstrictor. This is probably because the presence of vasoconstrictor increases the anesthetic effect, reducing the onset time, and prolonging duration. In the present study, this reduction was more than one-third part for lidocaine with epinephrine group, being significantly lower for bupivacaine with epinephrine group. This reduction could be considered clinically

Table 2. Comparison of Different Onset Times of Anesthetic Effect Between Study Groups

<table>
<thead>
<tr>
<th>Latency Time (s)</th>
<th>Lidocaine 2% Group</th>
<th>Lidocaine 2% With Adrenaline Group</th>
<th>Bupivacaine 0.5% Group</th>
<th>Bupivacaine 0.5% With Adrenaline Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>137.50</td>
<td>90</td>
<td>152.50</td>
<td>130.00</td>
<td>—</td>
</tr>
<tr>
<td>Mean ± SD (bupivacaine 0.5% with or without adrenaline group)</td>
<td>—</td>
<td>—</td>
<td>174.11 ± 81.17</td>
<td>138.71 ± 49.51</td>
<td>.040*</td>
</tr>
<tr>
<td>Mean ± SD (lidocaine 2% with or without adrenaline group)</td>
<td>135 ± 39.05</td>
<td>94 ± 25.08</td>
<td>—</td>
<td>—</td>
<td>.000*</td>
</tr>
<tr>
<td>Typical mean error</td>
<td>6.359</td>
<td>4.272</td>
<td>15.860</td>
<td>9.358</td>
<td>—</td>
</tr>
<tr>
<td>95% CI (lower limit-upper limit)</td>
<td>119.81–145.90</td>
<td>81.23–98.77</td>
<td>141.57–206.65</td>
<td>119.51–157.91</td>
<td>—</td>
</tr>
</tbody>
</table>

Cl, confidence interval.
Values are represented as the mean ± SD in seconds.
*t test (CI 95%), P < .05.

Table 3. Characteristics of SO2 With Lidocaine 2% Groups (With or Without Adrenaline) or Bupivacaine 0.5% groups (With or Without Adrenaline) Undergoing Digital Block

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine 2% Group (n = 28)</th>
<th>Lidocaine 2% With Adrenaline Group (n = 28)</th>
<th>Bupivacaine 0.5% Group (n = 28)</th>
<th>Bupivacaine 0.5% With Adrenaline Group (n = 28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinfiltration</td>
<td>98.69 ± 1.38%</td>
<td>98.39 ± 1.34%</td>
<td>98.35 ± 1.14%</td>
<td>98.25 ± 1.10%</td>
<td>.111*</td>
</tr>
<tr>
<td>30 s</td>
<td>98.80 ± 1.38%</td>
<td>97.86 ± 1.68%</td>
<td>98.75 ± 1.04%</td>
<td>97.28 ± 1.36%</td>
<td>.125*</td>
</tr>
<tr>
<td>1 min</td>
<td>98.79 ± 1.43%</td>
<td>97.14 ± 1.11%</td>
<td>97.96 ± 1.13%</td>
<td>95.96 ± 1.24%</td>
<td>.226*</td>
</tr>
<tr>
<td>3 min</td>
<td>97.95 ± 0.67%</td>
<td>96.47 ± 1.02%</td>
<td>97.86 ± 0.98%</td>
<td>94.71 ± 1.01%</td>
<td>.066*</td>
</tr>
<tr>
<td>5 min</td>
<td>97.90 ± 1.23%</td>
<td>95.32 ± 0.98%</td>
<td>98.03 ± 0.89%</td>
<td>94.75 ± 1.23%</td>
<td>.041*</td>
</tr>
<tr>
<td>10 min</td>
<td>98.10 ± 1.57%</td>
<td>95.90 ± 1.33%</td>
<td>97.82 ± 1.23%</td>
<td>95.89 ± 1.27%</td>
<td>.045*</td>
</tr>
<tr>
<td>20 min</td>
<td>98.28 ± 0.98%</td>
<td>97.32 ± 1.00%</td>
<td>98.15 ± 1.03%</td>
<td>97.25 ± 1.14%</td>
<td>.124*</td>
</tr>
<tr>
<td>30 min</td>
<td>98.43 ± 1.09%</td>
<td>97.90 ± 0.67%</td>
<td>98.29 ± 1.13%</td>
<td>97.64 ± 0.94%</td>
<td>.116*</td>
</tr>
<tr>
<td>60 min</td>
<td>98.29 ± 1.11%</td>
<td>98.43 ± 0.99%</td>
<td>98.54 ± 0.96%</td>
<td>98.18 ± 1.48%</td>
<td>.119*</td>
</tr>
<tr>
<td>Mean</td>
<td>97.34 ± 2.34%</td>
<td>98.23 ± 0.86%</td>
<td>98.16 ± 1.04%</td>
<td>96.65 ± 1.5%</td>
<td>.126*</td>
</tr>
</tbody>
</table>

Values are represented as the mean ± SD.
*One way analysis, P < .05.
significant for lidocaine with epinephrine blocks, especially in the emergency department. However, this observation has shown contradictory results in other clinical trial that compared anesthetics with or without a vasoconstrictor in DNB using pin-prick sensation loss. Sonohata et al analyzed the onset time in 9 healthy subjects (18 fingers) who were injected with 3 mL of lidocaine 1% in the middle point of the digital palmar space of the third finger, and lidocaine 1% with epinephrine 1:100,000 in the same finger of the other hand. The mean onset time obtained was also significantly shorter for the anesthetic solution with vasoconstrictor (4.60.85 vs 2.80.83 minutes; \( P, .05 \)). The registered differences in onset time may be because of a lower concentration of lidocaine used compared with our study. Other studies with the same methodology using bupivacaine and lidocaine with or without vasoconstriction or a mixture of both at different concentrations did not show significant differences with respect to the onset of action. Only one study compared the effect of three of the four anesthetic solutions used in our study, unfortunately it was not possible to establish any comparison because they only analyzed the mean time of anesthesia in each of the groups, without determining the onset time.

There are others factors that can condition the pharmacokinetics of local anesthetics and therefore its onset time. These factors depend on the one hand, on the chemical structure of the molecule, volume, and concentration infused, and on the other hand, on characteristics of the medium (tissue pH) and the anatomic location where it is administered. With respect to chemical structure, the amine group is the one that conditions the \( pK_a \) of the anesthetic base (pH at which the anesthetic solution is in 50% dissociation). Thereby, the closer the \( pK_a \) of the anesthetics is to physiological pH, the greater its speed of action will be. The \( pK_a \) of the anesthetic bases used in this study was 7.9 for lidocaine and 8.1 for bupivacaine, which explains why bupivacaine had a significantly longer onset time than lidocaine.

The pH of the solution and the medium in which the anesthetics is infiltrated may also condition the onset time in a way that the more acidic the solution is, more difficult it is for the anesthetics to be absorbed. The pH of anesthetic solutions ranges between 5.5 and 7.0, and it is lower for solutions with a vasoconstrictor, because the sodium bisulfite used to make the solution with epinephrine stable decreases the pH. The mean pH values recorded for the solutions used in our study were

![Safety curve in patients receiving Lidocaine 2% infiltration](image1.png)

![Safety curve in patients receiving Lidocaine 2% with epinephrine 1:100,000 infiltration](image2.png)

![Safety curve in patients receiving Bupivacaine 0.5% infiltration](image3.png)

![Safety curve in patients receiving Bupivacaine 0.5% with epinephrine infiltration](image4.png)

Figure 2. Comparison of SO\(_2\) curve in study patients. This figure is available in color online at www.jopan.org.
6.1 ± 0.3 for lidocaine, 4.4 ± 0.7 for lidocaine with vasoconstrictor, 6.0 ± 0.4 for bupivacaine, and 4.5 ± 0.8 for bupivacaine with vasoconstrictor. Despite these differences, the onset time from the clinical point of view was not considerably different between the groups. Another interesting aspect is that although the anesthetic solutions with vasoconstrictor have a pH more acidic than solutions without vasoconstrictor used, these were the ones that showed a shortest mean onset time.

Another aspect that conditions the differences recorded in the different studies regarding the onset time after DNB could be because of anatomic characteristics of the location where the anesthetic solution is infiltrated. Fingers and toes have nerve fibers of small diameter, which explains why in DNB, the Aδ and unmyelinated C-fibers, whose role is to transmit the pain and thermal stimuli, become blocked in a short period of time compared with the onset time reached after regional or trunk blocks (major nerve blocks). On the other hand, the method used in the different studies that analyzed the onset time of anesthetics was the pin-prick or needle-prick test, and in some cases there are no details of the characteristics of the device used; in other cases, it was the patient or participant who conducted the test, with the consequent bias in the results.

Regarding peripheral SO₂, and as in similar studies that have used this parameter, there were no significant differences between any of the groups analyzed. SO₂ does not seem to be considerably modified by the effect of the vasoconstrictor, which would be explained by the fact that local amide anesthetics in general, and lidocaine in particular, have a sympatholytic effect that partially counteracts the vasoconstrictor effect of epinephrine, maintaining the SO₂ within normal levels. The results of some prospective studies suggest that even at higher concentrations of epinephrine (1:80.000), the digital arterial blood flow was not considerably modified and the vascularization of the finger was not jeopardized. Likewise, in the studies that analyzed the fingertip capillary blood parameters as oxygen partial pressure (PO₂) and SO₂ after anesthetic blocks with vasoconstrictor, the subjects did not experience any problems with perfusion of the digits.

In terms of gender,
we have not registered differences in SO₂ recorded in the lidocaine 2% with epinephrine group with respect to the other groups. In the male group, SO₂ remained stable during the study among the groups; however, two females in the lidocaine 2% with epinephrine group showed a decrease in SO₂ at 10 minutes after injection to 94% with a punctual decrease at 20 minutes. Similar studies have shown that between 10 and 20 minutes after administration of 1% lidocaine with vasoconstrictor (1:100,000), PO₂, SO₂, or digital artery blood flow decreased transiently within 60 to 90 minutes in digits infiltrated.⁵,¹⁴⁻¹⁶ We consider that this nonsignificant decrease in SO₂ in 2% lidocaine with epinephrine group is not gender related and could be because of personal variations such as more sensitivity to epinephrine.

In the emergency department, patients often present with injured digits that may require DNB. In certain settings, it may be beneficial for the anesthetic solutions to have a rapid onset of action, vasoconstrictive properties, and adequate duration of anesthesia. In view of the results of the present study, we consider that in patients with injured digits, DNB with lidocaine with epinephrine (1:100,000) provides a short onset time and can be the ideal option. In the same way in elective ambulatory surgery, when it is necessary to increase the length of time to pain relief, bupivacaine with epinephrine (1:200,000) may be the best option. In the present study, SO₂ remained within normal values after DNB and no adverse effects were recorded for any of the anesthetic solutions. So we consider that in healthy subjects, the use of anesthetic solutions with epinephrine for DNB can be considered safe.

**Limitations of the Study**

Undoubtedly, our research has some limitations. It is important to take into account that the abolition of discontinuous pain stimuli as the ones produced by pin prick takes place earlier than the abolition of continuous pain stimuli, such as a needle prick or the one generated by a cut with a scalpel. Thereby, we consider that the anesthetic onset time obtained with the pin-prick test is slightly shorter than the time needed to perform invasive procedures with complete pain abolition.
Conclusions

The addition of epinephrine for DNB significantly reduced the onset time of the anesthetic solutions used in the present study. This reduction could be considered clinically significant especially for lidocaine with epinephrine 1:100,000. Both anesthetic solutions with vasoconstrictor effect can provide benefits and can be an effective alternative when vasoconstrictive action or prolonged duration of anesthesia be required. However, it is likely that the anesthetic onset time obtained with the pin-prick test is slightly shorter than the time needed to perform invasive procedures. The normal values of SO₂ registered after DNB with the anesthetic solutions used show that its use can be considered safe.

Acknowledgment

The authors give special thanks to the Area Clínica de Podología of the Universidad de Sevilla for its logistic support.

References