Buffered local anesthetics reduce injection pain
and provide anesthesia for up to 5 hours

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Abstract

Objective: Buffered local anaesthesia is widely used in many specialties as it is believed to reduce pain during injection. However, solutions containing high concentrations of lidocaine and adrenaline cannot currently be buffered due to precipitation. The aim of the present study was to investigate whether the use of non-buffered local anesthetics with higher concentrations of lidocaine and epinephrine for longer operations is justified, bearing in mind the amount of injection pain to which the patient is subjected, or whether buffered local anesthetics are just as effective.

Methods: Three preparations of local anesthetics were injected subcutaneously into the forearm of 12 healthy adult volunteers: non-buffered lidocaine (20 mg/ml) + epinephrine (12.5 µg/ml), pH ≈4.2, buffered lidocaine (10 mg/ml) + epinephrine (5 µg/ml) pH ≈7.4, and non-buffered lidocaine (20 mg/ml) pH ≈6.0. Injection pain, and onset and duration of anesthesia, were estimated using a numerical rating scale.

Results: Much less pain was experienced on injection when using buffered lidocaine + epinephrine than the non-buffered mixture (p < 0.001). The onset of anesthesia was recorded within 4 min in all subjects, and was similar with all three preparations. The duration of anesthesia was much longer for the lidocaine + epinephrine preparations (buffered 5.6 hours and non-buffered 6.6 hours) than for lidocaine alone (1.3 hours).

Conclusions: Buffered lidocaine + epinephrine appears to reduce levels of pain on injection, and provides anesthesia for at least 5 hours.
Introduction

Local anesthesia is widely used to minimize pain during surgery, and the combination of lidocaine and epinephrine is frequently used for local anesthesia in plastic surgery to reduce perioperative bleeding. The use of epinephrine has been shown to prolong the analgesic effect, as the lidocaine does not diffuse out of the region as quickly due to the vasoconstrictive effect of epinephrine (Larrabee et al., 1987, Fink et al., 1978).

The pH of lidocaine (without epinephrine) in preparations used for local anesthesia varies between 3.5 and 7.0 (Cepeda et al., 2010), and local anesthetics combined with epinephrine often have a low pH (3.5) to prolong their shelf life. However, the physiological pH in tissue fluid is about 7.35-7.45. Lidocaine is therefore more acidic than tissue, which increases the pain experienced by the patient during injection. After the anesthetic is injected, it is buffered by tissue fluids to neutral pH (Strichartz et al., 1990). Increasing the pH of a local anesthetic by buffering the solution is known to decrease the pain on injection (Cepeda et al., 2010).

However, only preparations containing low concentrations of lidocaine and epinephrine can be buffered as precipitation takes place at higher concentrations. It is a common belief among surgeons that preparations with low concentrations of lidocaine and epinephrine (e.g. 10 mg/ml lidocaine + 5 µg/ml epinephrine) do not have the same anesthetic effect and duration as preparations with higher concentrations (e.g. 20 mg/ml lidocaine + 12.5 µg/ml epinephrine). The type of surgery, the duration of the procedure and the risk of bleeding affect the choice of local anesthetic, and surgeons therefore feel that they must choose between more highly concentrated local anesthetics and a weaker buffered one. This has led to a tendency for buffered local anesthetics to be used for short, simple operations, and non-buffered preparations for longer, more complicated operations. However, no systematic studies have been carried out to investigate the properties of weaker buffered local anesthetics vs. stronger non-buffered local anesthetics.
Purpose

This study was performed in order to investigate/determine whether the use of non-buffered local anesthetics with higher concentrations of lidocaine and epinephrine for longer operations is justified, bearing in mind the amount of injection pain to which the patient is subjected, or whether buffered local anesthetics are just as efficient/effective.

Methods

Subjects

Twelve adult volunteers were included in the study. Presumptive participants were excluded if they had any medical condition that contraindicated the administration of local anesthesia with epinephrine, such as heart conditions or previous allergic reaction to local anesthetics. One subject was taking medication for hypertension, while the others had no known medical conditions, and were considered healthy (table 1).

Table 1. Characteristics of the 12 participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Women/men</td>
<td>7/5</td>
</tr>
<tr>
<td>Median age (y) (range)</td>
<td>45 (32-72)</td>
</tr>
<tr>
<td>Median resting pulse before administration of local anesthetic (BPM) (range)</td>
<td>64 (48-86)</td>
</tr>
<tr>
<td>Median maximum pulse during administration of local anesthetic (BPM) (range)</td>
<td>72 (55-96)</td>
</tr>
<tr>
<td>Median pulse 30 min after administration of local anesthetic (BPM) (range)</td>
<td>60 (51-70)</td>
</tr>
<tr>
<td>No. of patients without known disease</td>
<td>11</td>
</tr>
<tr>
<td>No. of patients using medication for hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>
Study protocol

The heart and lungs of each subject were auscultated before starting the procedure. The subject was then asked to rest for 10 minutes in the prone position to allow the resting pulse and blood pressure to stabilize before injection of the anesthetics. Heart rate was monitored continuously 10 min before and during the procedure.

Three marks were made, 7 cm apart, to avoid interference between the injection points on the volar side of one of the subject’s forearms indicating the sites of injection. The subject was instructed on the use of the numerical rating scale (NRS) and asked to assess the level of pain when the skin was pinched with a pair of tweezers (Stille Tissue forceps, Stille AB, Torshälla, Sweden) at the three sites of planned injection. The scale extends from 0 (no pain) to 10 (unbearable pain).

The following three infiltration anesthetics were chosen as they are frequently used for local anesthesia during surgical procedures.

1. Lidocaine (10 mg/ml) + epinephrine (5 µg/ml) (Xylocain Adrenalin®, AstraZeneca, Södertälje, Sweden) with a pH ≈4.2, buffered to pH ≈ 7.4 using sodium bicarbonate 50 mg/ml (Natriumbikarbonat Fresenius Kabi®, Fresenius AG Bad Homburg, Germany) at a ratio of 5 to 1, denoted “buffered L+E”.
2. Lidocaine (20 mg/ml) + epinephrine (12.5 µg/ml) (Xylocain Dental® Adrenalin, Dentsply Ltd., York, PA, USA), pH of ≈4.2, denoted “non-buffered L+E”.
3. Lidocaine (20 mg/ml) (Lidokain®, Mylan Hospital AS, Oslo, Norway), pH ≈ 6.0, denoted “non-buffered L”.

The anesthetic solutions were preheated to 37 °C before injection into the subcutaneous tissue. The volume used was 0.5 ml as this represents a clinically significant amount, without the risk of “interference” between the injection locations. All three injections were administered on the same occasion. The type of anesthetic injected at each site was randomized between the subjects using MS Excel and the function Rand. The anesthetics
were infiltrated as uniformly as possible by the same surgeon within a 1.5 cm$^2$ area in order to achieve standardized anesthesia.

After administration of the three local anesthetics the subjects were asked to assess the pain during injection using the NRS. The subjects were then pinched every 30 seconds at each site until the level of pain was rated as zero on three consecutive occasions, to determine the onset of anesthesia. Pinching was then performed 10 and 20 min after injection, and then every 30 min until sensation had returned, i.e. the pain was scored as greater than 0 using the NRS.

Figure 1. Illustration of the injection of the three local anesthetics on the forearm of the subjects.

**Ethics**

The experimental protocol for this study was approved by the Ethics Committee at Lund University, Sweden. The research adhered to the tenets of the Declaration of Helsinki as amended in 2008. All the subjects participating in the study were given verbal and written information about the study, and the voluntary nature of participation. All subjects gave their informed written consent.
Financial support

This study was supported by the Swedish Government Grant for Clinical Research (ALF), the Skåne University Hospital (SUS) Research Grants, the Region Skåne County Council Research Grants, Crown Princess Margaret’s Foundation (KMA), the Foundation for the Visually Impaired in the County of Malmöhus, The Nordmark Foundation for Eye Diseases at Skåne University Hospital, the Diabetes Society of South-West Skåne, and the Swedish Eye Foundation.

Limitations

Ideally, it would have been interesting to study all the preparations at various concentrations, especially buffered and non-buffered L+E. However, this was not possible due to the limited area of the forearm, and the number of injections that could ethically be given to each subject.

It would also have been an advantage to have had a reference area outside the anesthetized area, or to have used a negative control, for example, an injection of 5% sodium chloride, but exposing the subjects to pain levels of about 4, repeatedly over a few hours, was not considered ethically acceptable.

Calculations and statistics

Calculations and statistical analysis were performed using GraphPad Prism 7.2 (GraphPad Software Inc., San Diego, CA, USA). Statistical analysis was performed using Friedman’s test with Dunn’s multiple comparison test. Significance was defined as: p<0.05 (*), p<0.01 (**) and p>0.05 (not significant, n.s.).
**Results**

**Pain on injection**

Injection with buffered L+E (pH ≈7.4) was the least painful, and the subjects assessed the pain to be 2 on the NRS (range 1-3). Injection of the non-buffered L+E (pH ≈4.2) was significantly more painful NRS score 4 (3-5) (p<0.05). The injection of non-buffered L, with a pH ≈6.0, was also more painful than buffered L+E (NRS 3 (1-6), p<0.05). The results are shown in Figure 2.

![Figure 2. Pain on injection of three local anesthetics in the forearm of healthy subjects, measured using the numeric rating scale (NRS). It can be seen that the preparation buffered to the physiological pH of tissue (≈7.4) elicited the least pain on injection.](image-url)
Onset and duration of anesthesia

The onset of anesthesia occurred within 4 min in all the subjects, and was similar for the three preparations (Figure 3A). The duration of anesthesia was much longer for the L+E preparations (5.6 (2.3 to 8.8) hours for buffered L+E and 6.6 (4.3 to 9.8) hours for non-buffered L+E) than for lidocaine alone (1.3 (0.8 to 3.3) hours) (Figure 3, see separate file).

Figure 3. Onset and duration of the anesthetic effect of the three local anesthetics (A, B, C), assessed on the NRS. Data are shown in scatterplots where a line is drawn through the median values. It can be seen that the duration of anesthesia was considerably longer with the two anesthetics containing epinephrine (5.6 and 6.6 h) than with lidocaine alone (1.3 h).

Figure 4. Onset (A) and duration (B) of local anesthesia. Onset of anesthesia was defined as a numeric rating scale (NRS) of less than one on three consecutive occasions 30 seconds apart.

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Discussion

The results of this study show that injection pain was significantly lower when administering buffered L+E, than non-buffered L+E. This is consistent with previous findings that buffering reduces pain during the administration of local anesthesia (Cepeda et al., 2010).

The duration of anesthesia with the buffered L+E and the non-buffered L+E was 5.6 hours and 6.6 hours, respectively. The difference between these was statistically significant, but has little clinical relevance for surgical procedures shorter than 5.6 hours. There was no statistically significant difference between the onset of anesthesia with the three agents (within 4 mins), although the results indicate a slight clinical difference. As less pain is experienced when administering buffered local anesthetics, these are recommended when treating children or adults with special needs, and are also advantageous in sensitive areas of the body, such as the face. The higher concentration of epinephrine (as in the non-buffered L+E) may be advantageous during surgical procedures when bleeding must be minimized, or when the patient is taking anticoagulants, since this has been shown to induce slightly more hypoperfusion (Sheikh et al., 2017).

The disadvantage of buffered lidocaine is that its shelf life is only one day, and new mixtures must be prepared each day. However, the benefits to the patient of buffered lidocaine should be weighed against the economic and environmental effects of producing buffered anesthetics surplus to requirements.

The method used to measure pain in this study was pinching the skin with tweezers. This only provides information on the superficial response to the anesthetics studied, and it is therefore not possible to draw any conclusions on the onset and duration of anesthesia at deeper levels in the tissue. Furthermore, no surgical procedure was performed, which might also have affected the properties of the anesthetics in the tissue. Additional studies are required to investigate the characteristics of local anesthetics in other parts of the body, and the effects deeper in tissue.
In conclusion, a buffered local anesthetic containing low concentrations of lidocaine and epinephrine seems to have the same anesthetic effect and duration as an unbuffered solution of lidocaine and epinephrine at higher concentrations, but causes less pain on injection. The benefits to the patient, in terms of reduced injection pain, thus indicate that such preparations could preferably be used for surgical procedures lasting up to 5 hours.

Acknowledgements

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References


