Effect of pH modification by bicarbonate on pain after subcutaneous lidocaine injection

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Objective: To quantify the pain experienced on subcutaneous injection of lidocaine, lidocaine with sodium bicarbonate ($NaHCO_3$) and saline.

Design: A double-blind randomized prospective study.

Setting: A clinical research unit in a university-affiliated hospital.

Participants: Forty-two healthy adult volunteers who did not have a history of adverse reaction to lidocaine or peripheral neuropathy and were not pregnant. The study was performed in two phases. In Phase 1, 1 mL each of thee solutions (2 mL of 8.4% $NaHCO_3$ in 20 mL 1% lidocaine, 2 mL saline in 20 mL lidocaine and saline alone) were injected by an investigator, blinded as to the identity of the solutions, in random order to five volunteers to measure onset and duration of anesthesia and the perceived pain on injection. In Phase 2, 37 volunteers were injected with the three solutions in random order, by an investigator blinded as to the identity of the solutions.

Main Outcome Measure: Pain on injection measured with the visual analogue scale.

Results: There were no clinically significant differences between onset and duration of action of lidocaine with and without $NaHCO_3$, as determined by Kruskal–Wallis one-way analysis of variance and the Wilcoxon signed-ranks test. Injection of lidocaine with $NaHCO_3$ was significantly less painful than injection of plain lidocaine ($p = 0.041$). Injection of saline was the most painful.

Conclusion: The addition of $NaHCO_3$ to lidocaine produces significant reduction in pain experienced on injection without significantly affecting the onset or duration of action.

Objectif : Quantifier la douleur ressentie au moment de l'injection sous-cutanée de lidocaïne, de lidocaïne avec bicarbonate de sodium ($NaHCO_3$) et de solution saline.

Conception : Étude prospective randomisée à double insu.

Contexte : Service de recherche clinique d'un hôpital affilié à une université.

Participants : Quarante-deux bénévoles adultes en bonne santé qui n'avaient pas d'antécédents de réaction indésirable à la lidocaïne ou de neuropathie périphérique, et qui n'étaient pas enceintes. L'étude s'est déroulée en deux temps. Au cours de la phase 1, on a injecté 1 mL de chacune des trois solutions (2 mL de $NaHCO_3$ à 8,4 % dans 20 mL de lidocaïne à 1 %, 2 mL de solution saline dans 20 mL de lidocaïne et solution saline seulement). Les injections ont été effectuées par un chercheur qui ne connaissait pas la nature des solutions et les a injectées au hasard à cinq bénévoles afin de mesurer le début et la durée de l'anesthésie et la douleur perçue au moment de l'injection. Au cours de la phase 2, 37 bénévoles ont reçu les trois solutions qui leur ont été injectées au hasard par un chercheur qui n'en connaissait pas la nature.

Principale mesure des résultats : Douleur au moment de l'injection, mesurée selon l'échelle analogique visuelle.

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RÉSULTATS : Il n'y avait aucune différence significative sur le plan clinique entre l'apparition et la durée de l'effet de la lidocaïne avec et sans $NaHCO_3$, selon l'analyse de variance à un critère de classification de Kruskal–Wallis et le test de Wilcoxon pour observations appariées. L'injection de lidocaïne avec du $NaHCO_3$ était beaucoup moins douloureuse que l'injection de lidocaïne pure (p = 0,041). L'injection de solution saline était la plus douloureuse.

CONCLUSION : L'ajout de $NaHCO_3$ à la lidocaïne réduit considérablement la douleur ressentie au moment de l'injection sans affecter pour la peine l'apparition ou la durée de l'effet.

To decrease costs, patient risks and the inconveniences associated with general anesthesia, the number of outpatient surgical procedures, particularly those performed under local anesthesia, has been increasing. However, the use of local anesthetics is not without morbidity. A burning pain is commonly experienced on injection and can make the injection of a large amount of local anesthetic very unpleasant for the patient. The pain can be attributed to many factors including the acidity of the local anesthetic. Many surgeons and dentists claim to have decreased this initial pain by buffering the local anesthetic with sodium bicarbonate ($NaHCO_3$). Although several studies[1–8] have demonstrated a reduction in pain on injection of buffered anesthetics, the studies contained several design flaws. We critically reviewed the literature focusing on the issue of pH adjustment of lidocaine to reduce pain on infiltration. All studies[1–5] identified a reduction in perceived pain with injection of buffered solutions. However, in some studies only 0.1 mL of solution was injected. In others the pain scale was used after as many as five injections had been given rather than between each injection. Finally, not all studies allowed the participants to serve as their own controls. These flaws compromise the validity of these studies.

We, therefore, set out to test whether there is a difference in perceived pain on injection of lidocaine with or without the addition of $NaHCO_3$ in a study that corrected these flaws in design.

METHODS

Ethical approval was obtained before the start of the study. Forty-two healthy adult volunteers were recruited. Exclusion criteria were a history of adverse reaction to lidocaine, pregnancy and peripheral neuropathy. The study was performed in two phases.

Phase 1

This pilot phase was performed to test the onset and duration of anesthesia for each solution and to detect any logistical problems, so that the phase 2 study could be altered accordingly. The solutions were prepared by the first investigator as follows: solution 1 — 2 mL of 8.4% $NaHCO_3$ was added to 20 mL of 1% lidocaine with preservative to produce a 1:10 dilution; solution 2 — 2 mL of sterile normal saline without preservative was added to 20 mL of 1% lidocaine to obtain the same concentration of drug as in the buffered solution; solution 3 — sterile normal saline was used as placebo for comparison of injection pain and duration of action against solutions 1 and 2.

The pH and osmolality of each solution were measured. For each subject, the first investigator drew up 1 mL of each of the three solutions at room temperature in 1 mL tuberculin syringes labelled A, B and C. The sequence of injections was randomized to eliminate any order effect. The syringes were then passed to the second investigator who, along with five volunteers, was blinded to the identity of the contents.

Each volunteer was treated in a similar manner. The skin of the volar aspect of the non-dominant forearm was prepared with an alcohol swab and allowed to dry. The injection sites were marked near the antecubital fossa 4 cm apart, forming a triangle. With a 27-gauge needle, 1 mL of each solution was injected over 20 to 25 seconds into the subcutaneous tissue. Five minutes were allowed to elapse between injections. Following each injection, the volunteer was asked to indicate the amount of pain perceived (ranging from no pain to extreme pain) on a 100-mm visual analogue scale (VAS), a tool used to graphically quantify pain.[9] To test the onset of anesthesia, cold stimulus in the form of an alcohol swab was used. Cold stimulus has been shown to be a sensitive way to test anesthesia without introducing the morbidity associated with a pin prick. Each injection site was tested at 30-second intervals up to 3 minutes or until anesthesia occurred. Each site was then tested for duration of anesthesia by the same method every 20 minutes for 3 hours.

Phase 2

The three solutions were prepared in the same manner as in phase 1 and transferred to 1-mL syringes. Once again, the sequence of injection was randomized for each volunteer. Thirty-seven blinded volunteers were then marked and injected as in phase 1 by the blinded second investigator. The VAS was again administered between injections.

Statistical analysis

Initially, the resulting data were not normally distributed. As a result, to take a conservative approach, nonparametric analyses were conducted. Kruskal–Wallis one-way analysis of variance and a Wilcoxon signed-ranks tests for matched samples were used for statistical analysis.

Results

Phase 1

Descriptive statistics were calculated. All five volunteers were women, ranging in age from 23 to 43 years (mean 31 years). VAS pain scores are shown in Table I. The measured pH and osmolality of the three solutions are listed in Table II.

The onset and duration of anesthesia were as follows: solution 1— onset 30 seconds in all five volunteers, duration 1.5 hours, with one volunteer reporting loss of anesthesia at 3.5 hours; solution 2 — onset 30 seconds in three volunteers, 60 seconds in one and 90 seconds in one, duration from 1.5 to 5 hours; solution 3 — no anesthesia in two volunteers, 30 seconds in two and 90 seconds in one. The three volunteers who experienced anesthesia with normal saline all regained sensation in less than 20 minutes.

Phase 2

Of the 37 volunteers, 23 (62%) were female. They ranged in age from 21 to 56 years (mean 35 years). The results of the VAS for the pain perceived on injection are illustrated in Fig. 1. Using the Kruskal–Wallis one-way analysis of variance, we found a statistically significant difference between the three solutions ($p < 0.0001$). The Wilcoxon signed-ranks test for matched samples revealed a significant difference between each pair of solutions as follows: between lidocaine with and without $NaHCO_3$, $p < 0.001$; between lidocaine and saline, $p < 0.001$; and between lidocaine with $NaHCO_3$ and saline, $p > 0.001$.

Further analysis revealed no effect of gender or order of presentation of solutions (i.e., which solution was injected first) on the amount of pain perceived ($p = 0.966$ and $p = 0.350$ respectively). However, older volunteers reported less pain overall than younger volunteers ($p = 0.017$). The injection of normal saline was found to be the most painful in 21 volunteers. Five volunteers reported the injection of alkalinized lidocaine to be the most painful and the remaining seven, plain lidocaine. Interestingly, four volunteers reported no difference in pain sensation between any of the three solutions injected. The reason for these interpersonal differences is unknown.

No serious reactions to the injections or solutions were identified. A few volunteers reported local bruising at the injection site, itching (lasting seconds) and numbness in the distribution of a regional cutaneous nerve, which resolved when the local anesthetic lost its effect.

Table I

Results of Phase 1 Study of Three Solutions Used to Test Effect of Bicarbonate With Lidocaine on Pain Sensation

Solution	Mean (and range) VAS score, mm
Lidocaine with sodium bicarbonate	22 (0–69)
Lidocaine alone	30 (4–81)
Normal saline	41 (15–67)

VAS = visual analogue scale

Table II

pH and Osmolality of the Three Solutions Used to Test for Pain After Subcutaneous Injection

Solution	pH	Osmolality, mOsm
Lidocaine with sodium bicarbonate	7.82	474
Lidocaine alone	6.79	303
Normal saline	6.50	295

Discussion

The phase 1 results revealed that the onset and duration of anesthesia were not compromised by the alkalinization of lidocaine. The onset of anesthesia with buffered lidocaine was within 30 seconds in all subjects; however, the onset of anesthesia alone for two subjects took longer than 30 seconds. Although these are small numbers, the rapidity of the onset of anesthesia with the addition of bicarbonate has been demonstrated previously.[3,6,7,10–12] It has been postulated that a more alkaline pH increases the diffusion capacity of the anesthetic agent, thereby accelerating its onset of action.

Several studies have found that buffered lidocaine solutions had the same duration of action as plain lido-

caine.[4,5] In our study, the duration of anesthesia varied between volunteers. However, since lidocaine with and without $NaHCO_3$ produced anesthesia lasting at least 1.5 hours, the ability to perform common surgical procedures, such as breast biopsies and hernia repairs under local anesthesia would not be adversely affected by the addition of bicarbonate to lidocaine.

The burning pain commonly experienced on injection of local anesthetics has been attributed to numerous factors, including intradermal rather than subcutaneous injection, injection with the anesthetic at room temperature rather than body temperature,[1,2,13,14] the presence of a vasoconstrictor (e.g., epinephrine),[3] tonicity of the solution different from that of the tissues,[4] a pressure effect from the rapid rate of injection, and the acidity of the solution.[4–6,13,14] To reduce the biases present and isolate the effect of pH on the amount of pain perceived, we controlled for the temperature of the solution and the rate of injection; all injections were subcutaneous, vasoconstrictors were eliminated and each volunteer served as his or her own control. Also, although the effect of the concentration of lidocaine on the pain experienced has been shown not to be a factor,[8] we used the same concentration of lidocaine for solutions 1 and 2.

The results of the phase 2 study revealed a significant reduction in the amount of pain experienced on injection of buffered lidocaine. The mechanism of this decrease in pain on injection is unclear but may be related to the altered pH. Lidocaine is a weak base. The lidocaine molecule acts by blocking the sodium channels in the nerve membrane. It diffuses through this lipoprotein membrane where it acts at the receptors of the sodium channels. Altering the pH of lidocaine increases the uncharged basic form of the drug, giving greater lipid solubility and allowing for greater diffusion of the drug through the membrane.[12] This results in more rapid block of more sensory fibres and a decrease in pain perceived. However, this mechanism does not explain the finding of Morris and Whish[5] that procaine, a more acidic compound, was less painful than lidocaine. They postulated that other intrinsic properties of the local anesthetic played an important role in reducing pain.

Another factor that was altered by the addition of $NaHCO_3$ to lidocaine was the osmolality. It is believed that increasing the tonicity of a solution above the tonicity of the space into which it is injected increases the pain experienced. The osmolality of both saline and plain lidocaine fell into the range of the normal osmolality of extracellular fluid (280 to 310 mOsm), into which they were injected. However, the buffered lidocaine had the highest osmolality of the three solutions, well out of the physiologic range. This does not explain the low pain scores for the buffered lidocaine and the high scores for normal saline. Therefore, the role that the osmolality of solutions plays in pain perception is uncertain.

The addition of $NaHCO_3$ to lidocaine produces a significant reduction in the pain experienced on injection without significantly affecting the onset or duration of action. This is presumably due to elevation of the pH of the solution. With the current trend toward outpatient surgery with local anesthesia, the ability to reduce the morbidity associated with the use of these agents would greatly benefit the patient. This study supports the routine addition of $NaHCO_3$ to lidocaine for surgical procedures performed under local anesthesia.

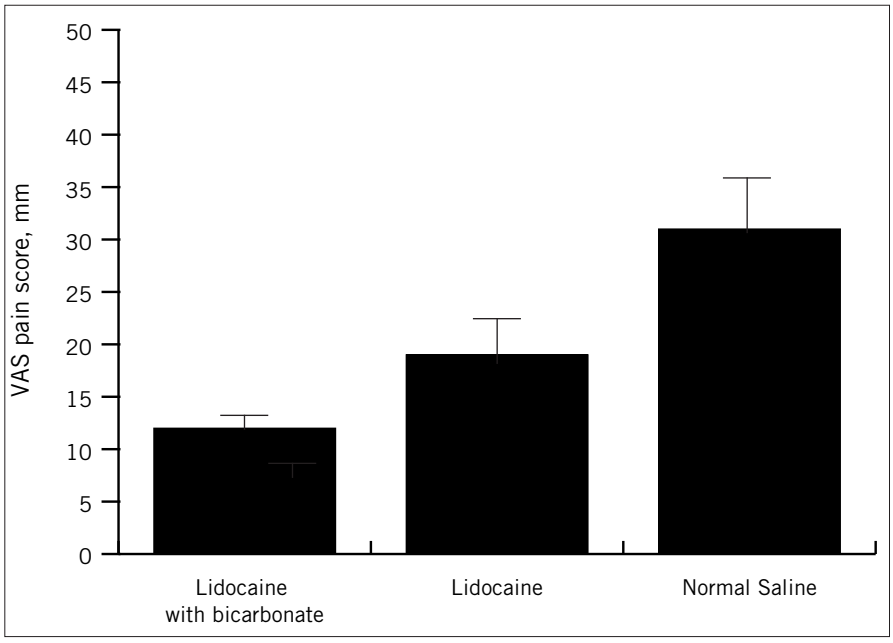

FIG. 1. Phase 2 study. Pain perceived by patients according to each of three solutions injected. VAS = visual analogue scale.

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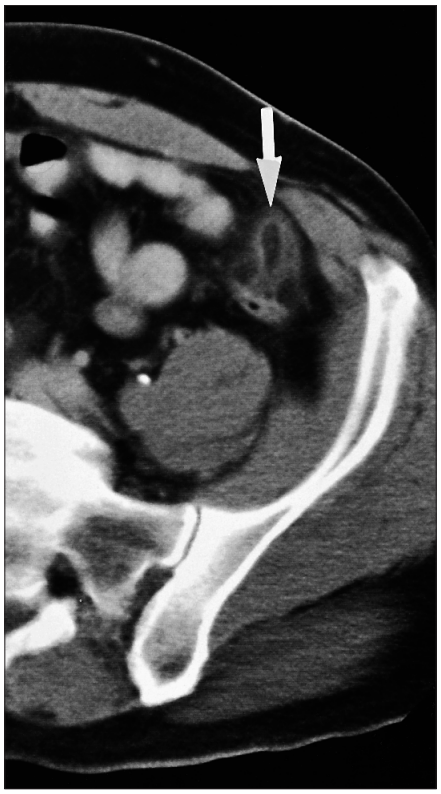
Radiology for the Surgeon
Chirurgie et radiologie

Case 7. Diagnosis

Primary epiploic appendagitis

There is a pedunculated mass in the left lower quadrant extending from the descending colon. The mass has a hyperattenuated peripheral rim with a central low density (fat). Depending on the location of the involved epiploic appendix, this entity may simulate diverticulitis, cholecystitis or appendicitis. The diagnosis is often only made at operation. Accurate radiologic diagnosis will allow conservative management, as a "leave-alone lesion."



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