

Buffered lidocaine and bupivacaine mixture – the ideal local anesthetic solution?

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The use of injectable local anesthetic solutions to facilitate pain-free surgery is an integral component of many procedures performed by the plastic surgeon. In many instances, a solution that has both rapid onset and prolonged duration of analgesia is optimal. A combination of lidocaine and bupivacaine, plain or with epinephrine, is readily available in most Canadian health care settings where such procedures are performed, and fulfills these criteria. However, commercially available solutions of both medications are acidic and cause a burning sensation on injection. Buffering to neutral pH with sodium bicarbonate is a practical method to mitigate the burning sensation, and has the added benefit of increasing the fraction of nonionized lipid soluble drug available. The authors report on the proportions of the three drugs to yield a neutral pH, and the results of an initial survey regarding the use of the combined solution with epinephrine in hand surgery.

Key Words: Buffering; Bupivacaine; Lidocaine

Lessening the pain of injection of local anesthetic (LA) is a desirable objective (1,2). Commercially available solutions of lidocaine are acidic, which causes pain upon injection (3,4). The merit of buffering lidocaine solutions to neutral pH as a method to eliminate this pain has been clinically advocated for decades (5-13). A 2010 Cochrane review of double-blinded randomized controlled trials that compared pH-adjusted lidocaine with unadjusted lidocaine concluded that buffering to neutral pH decreased pain on injection, and augmented patient comfort and satisfaction (14).

Lidocaine has a limited duration of action, which is sometimes desired in an LA but for many procedures is less than ideal. Bupivacaine has a much longer duration of action; however, due to its slow onset, it is not an ideal sole agent for procedural analgesia in most situations (15). The slow onset also results in a more painful injection when used as a sole agent because one cannot practically 'freeze ahead of the needle'; the recipient, therefore, feels the needle tip traversing throughout the tissues being infiltrated, a painful experience (1,2). In addition, bupivacaine, similar to lidocaine, is commercially supplied as an acidic solution, especially those prepared with epinephrine; the acidity contributes to injection pain.

However, combining these two amide LA agents in one syringe offers the clinician and patient the best effects of both drugs: the very rapid onset of lidocaine and the prolonged duration of bupivacaine. The present study aimed to investigate the amount of sodium bicarbonate required to neutralize the pH of these solutions, plain and with epinephrine, and to document some of the clinical properties of the use of these solutions in hand surgery.

METHODS

Part 1: laboratory work

Thirteen different solutions of lidocaine, bupivacaine and combinations of each, both plain and with epinephrine, were tested. The authors used 20 mL single-use vials available at their institution because they do not

Un mélange tampon de lidocaïne et de bupivacaine, l'anesthésique local idéal?

L'injection d'anesthésiques injectables locaux pour favoriser une opération sans douleur fait partie intégrante des nombreuses interventions réalisées par le plasticien. Dans bien des cas, une solution analgésique à action longue et rapide est optimale. Une bithérapie de lidocaïne et de bupivacaine, seule ou accompagnée d'adrénaline, disponible dans la plupart des milieux de santé canadiens où de telles interventions sont effectuées, respecte ce critère. Les solutions commerciales de ces deux médicaments sont toutefois acides et provoquent une sensation de brûlure à l'injection. L'utilisation d'un tampon de bicarbonate de sodium pour obtenir un pH neutre est pratique pour limiter la sensation de brûlure et a l'avantage supplémentaire d'accroître la fraction de médicament liposoluble non ionisé disponible. Les auteurs rendent compte des proportions des trois médicaments nécessaires pour obtenir un pH neutre et des résultats d'un sondage initial sur l'utilisation de la bithérapie combinée à l'adrénaline pour la chirurgie de la main.

contain preservatives that have been shown to affect the precipitation characteristics of LA solutions (16).

Twenty millilitres of each of the solutions were placed in clean 50 mL clear plastic containers at room temperature (approximately 21°C); 8.4% (1 mEq/mL) sodium bicarbonate (NaHCO₃) at room temperature was added by micropipette to the lidocaine solutions in 200 µL increments (to a maximum of 3 mL) and to the bupivacaine solutions in 20 µL increments (to a maximum of 0.2 mL). After the addition of each increment, solutions were manually shaken to ensure thorough mixing. They were then inspected for macroscopic precipitate formation against both white and black backgrounds. Measures were repeated three times for each solution and the results were averaged.

pH measurement: The pH levels of all solutions were measured both before and after each addition of NaHCO₃ using a pH meter (Accumet AB15, Fisher Scientific, Canada) calibrated to pH 4.00, 7.00 and 10.00 with certified buffer solutions from the manufacturer. The pH meter was standardized between each solution. Electrodes were rinsed with distilled water and blotted dry between each pH measurement to minimize the chance for contamination. Three samples of each solution were tested and the mean pH reported.

Optimal volume of NaHCO₃ required/ratio by volume/increase in nonionized fraction: The optimal volume of NaHCO₃ for each LA solution was determined as being the volume of NaHCO₃ needed to achieve near neutral pH without any macroscopic precipitate. Ratio by volume was then calculated: total volume of LA divided by optimal volume of buffer added. Relative increase in the nonionized fraction was determined by calculating ratio of ionized to nonionized ratio (LH+:L) at both initial pH and final pH using the Henderson-Hasselbalch equation:

$$\left(\frac{10^{\text{pKa} - \text{pH}}}{1 + 10^{\text{pKa} - \text{pH}}} = \frac{\text{ionized}}{\text{nonionized}} \right)_{\text{at initial pH}} / \left(\frac{10^{\text{pKa} - \text{pH}}}{1 + 10^{\text{pKa} - \text{pH}}} = \frac{\text{ionized}}{\text{nonionized}} \right)_{\text{at final pH}}$$

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TABLE 1
Solutions tested

Solution	pH, mean \pm SD		Optimal* volume of 8.4% NaHCO ₃ , μ L	Ratio by volume	Relative increase in nonionized fraction	LA:NaHCO ₃ (for 10 mL)
	Initial	Final				
1% Lidocaine	6.65 \pm 0.015	7.56 \pm 0.015	2000	10:1	8.1	9.09:0.91
1% Lidocaine/epinephrine	4.05 \pm 0.017	7.66 \pm 0.021	2200	9:1	4073.8	9.00:1.00
2% Lidocaine	6.42 \pm 0.47	7.22 \pm 0.05	800	25:1	6.3	9.62:0.38
2% Lidocaine/epinephrine	4.23 \pm 0.08	7.20 \pm 0.02	1200	17:1	933.3	9.71:0.29
0.25% Bupivacaine	5.83 \pm 0.074	7.14 \pm 0.032	60	333:1	20.4	9.97:0.03
0.25% Bupivacaine/epinephrine	4.4 \pm 0.061	6.71 \pm 0.03	100	200:1	204.2	9.95:0.05
0.50% Bupivacaine	5.55 \pm 0.09	6.82 \pm 0.02	40	500:1	18.6	9.98:0.02
0.50% Bupivacaine/epinephrine	4.26 \pm 0.14	6.53 \pm 0.04	100	200:1	186.2	9.95:0.05
Lidocaine/bupivacaine [†]	6.38 \pm 0.46	7.11 \pm 0.04	400	50:1	5.4	9.80:0.20
Lidocaine/bupivacaine/epinephrine [‡]	4.23 \pm 0.12	7.08 \pm 0.05	800	25:1	707.9	9.62:0.38

*Maximum volume of 8.4% sodium bicarbonate (NaHCO₃) added without causing precipitation; [†]2% lidocaine and 0.5% bupivacaine in a 1:1 ratio; [‡]2% lidocaine with 1:100,000 epinephrine and 0.5% bupivacaine with 1:200,000 epinephrine in a 1:1 ratio. LA Local anesthetic

Part 2: clinical survey

A series of adult patients undergoing either carpal tunnel release surgery or trigger digit surgery were surveyed. LA for all surgeries was a 50/50 solution of 0.5% bupivacaine with 1:200,000 epinephrine/2% lidocaine with 1:100,00 epinephrine buffered with 8.4% NaHCO₃ (Table 1). The time of administration was noted for each patient. They were asked to make a note of when they perceived pain at their surgical site, and were followed-up the next day with a telephone call to record their answer.

RESULTS

Part 1: laboratory work

Effect of alkalization on pH and precipitation: The mean initial pH of the five plain solutions was 5.55 to 6.65. Mean initial pH of the five solutions with epinephrine was lower (4.05 to 4.40) (Table 1). Adding 8.4% NaHCO₃ in volume increments of 200 μ L or 20 μ L, depending on the solution studied, increased all pH measures. The final pH ranges at which no precipitation occurred were near neutral, with a range of 6.53 to 7.66 (Table 1). Eventually, as more NaHCO₃ was added, macroscopic precipitation was observed in all solutions.

LA to NaHCO₃ volume ratios: The authors found that the LA to NaHCO₃ volume ratios (ratio by volume) required to increase the pH of the LA solutions without precipitation ranged from 9:1 to 500:1 (Table 1). All of the LA solutions with epinephrine required a lower ratio of LA to buffer (or more buffer per unit of LA).

Effect of alkalization on the relative increase in nonionized fraction: After alkalization, the nonionized fraction of lidocaine and bupivacaine increased in all LA solutions tested. The highest relative increases in the nonionized fraction of both lidocaine and bupivacaine were observed in the five solutions containing epinephrine (1% lidocaine/epinephrine, 2% lidocaine/epinephrine, 0.25% bupivacaine/epinephrine, 0.5% bupivacaine/epinephrine and lidocaine/bupivacaine/epinephrine). Only marginal increases in the nonionized fraction were observed in the corresponding plain solutions (1% lidocaine, 2% lidocaine, 0.25% bupivacaine, 0.5% bupivacaine, and lidocaine/bupivacaine) (Table 1).

Part 2: clinical survey

A total of 20 consecutive patients were surveyed (10 female, 10 male). The mean (\pm SD) duration of anesthesia reported was 11 h:18 \pm 215.5 min with a range of 5 h and 17 h:35 min. There was no significant difference between female and male patients.

DISCUSSION

There is no ideal LA solution for all applications; however, we have found the buffered combination solution of lidocaine and bupivacaine with epinephrine to be extremely versatile in plastic surgery. There are at least two theoretical advantages of neutral buffered versus acidic pH

solutions for LA injection: less painful infiltration and faster onset of anesthesia. Infiltration of nonbuffered acidic local anesthesia causes more pain than the injection of neutral buffered solutions (14). Neutralizing the solutions results in fewer hydrogen ions being injected – ions that appear to be responsible for the burning sensation reported by patients receiving acidic injections.

In addition, tissue anesthesia onsets faster when neutral solutions are injected. Compared with acidic solutions 'out of the bottle', more molecules of the drug are in the nonionized state in neutralized solutions. LA molecules must be in the nonionized state to penetrate both nerve cell sheaths and neural membranes (15). Once inside the cell, the nonionized drug gains a hydrogen ion, and this ionized form is responsible for the neural blockade. LAs are weak bases, and the relative proportion of each form of the drug depends on the solution pH and the drug's pKa (pH at which the nonionized and ionized fractions are at equilibrium). The relationship between pH and pKa is described by the Henderson-Hasselbalch equation:

$$\text{pKa} - \text{pH} = \log (\text{LH}^+)/(\text{L})$$

in which LH⁺ denotes the ionized fraction and L represents the nonionized fraction (15,17). Hence, raising the pH closer to pKa increases the fraction of the drug in the nonionized form, increasing the proportion of the administered dose that can enter neurons. This hastens anesthesia onset, reduces pain transmission and, thus, lowers pain perception on LA infiltration into tissues (3,5,8,15,18). Alkalinization also increases intracellular concentration of carbon dioxide, which effectively decreases intracellular pH. In more acidic intracellular pH, LAs exist more so in the ionized base form, actively blocking nerve cell sodium channels, thus preventing depolarization and the propagation of action potentials (15,18). The buffering effect on intracellular pH may, thus, also contribute to the more rapid onset of anesthesia reported with alkalinized solutions.

Epinephrine-containing LA solutions

The use of epinephrine-containing LAs in all body parts has a long, safe history in plastic surgery. Lalonde and Martin (19) and others (20,21) have provided a tremendously positive service to practitioners and the patients we serve by their work to debunk the traditional teaching of avoidance epinephrine-containing LAs in digits. It is the senior author's (TJB) opinion, that this can be safely extended to all 'end-artery' body parts – the nose, ears, penis, etc.

In the present study, we confirmed that LA solutions containing epinephrine were more acidic than their plain counterparts, consistent with previous reports (3,5,18). In addition to the lower initial pH, various additives, such as sodium metabisulphite and pH adjusters such as hydrochloric acid and sodium hydroxide contribute buffering capacity (16,18). Sodium metabisulphite is a strong antioxidant that

combines with epinephrine to form an inactive epinephrine sulfonate at pH >4, and is added to prevent the oxidation of epinephrine (7,22). All of the commercially prepared LAs with epinephrine required a greater amount of bicarbonate buffer to raise pH to near neutral without precipitation, and had the highest relative increase in the nonionized fraction with sodium bicarbonate buffering. Thus, there is greater clinical benefit of buffering these solutions compared with their plain or freshly prepared counterparts.

SUMMARY

The combined solution of 2% lidocaine with 1:100,000 epinephrine and 0.5% bupivacaine with 1:200,000 epinephrine in a 1:1 ratio, buffered with NaHCO₃, may be the ideal LA solution for practitioners to use in many clinical applications. A practical clinical application of the laboratory investigations presented in the present study is as follows:

- 10 mL syringe;
- 4.5 mL of 2% lidocaine with 1:100,000 epinephrine;
- 4.5 mL of 0.5% bupivacaine with 1:200,000 epinephrine; and
- 0.4 mL of 8.4% NaHCO₃.

This yields 9.4 mL of a combined solution, useful for many clinical applications. Obviously, volumes of each are halved for a 5 mL syringe, etc. This solution contains 0.96% lidocaine, 0.24% bupivacaine and 1:156,666 epinephrine. In our survey using this solution for 20 consecutive patients in hand clinic, a mean of 11 h:18 min of anesthesia was reported.

Areas for further work

We did not investigate the chemical stability of epinephrine in buffered solutions over time. There is little work that addresses stability, particularly for the alkalized lidocaine/bupivacaine combination, with only one published article reporting on the stability of epinephrine in such solutions (11). It is well documented that the chemical stability of epinephrine decreases significantly following alkalization

because increasing the pH of LA solutions favours the oxidation of epinephrine (3,8). What is unclear is the chemical stability of epinephrine in buffered solutions for prolonged periods of time (23-29). Until stability issues are better explained, we recommend buffering solutions containing epinephrine just before use.

Second, the theoretical advantage of more rapid anesthesia onset with buffered LA solutions has not been shown in our model of a combined lidocaine/bupivacaine solution. The magnitude and clinical significance of this effect requires investigation.

Third, our pilot survey involving 20 patients receiving the combined solution in hand surgery was just that, a pilot survey. A rigorous blinded study with appropriate statistical power would be ideal to more fully investigate the clinical characteristics of this solution.

The fourth area of investigation was in regard to epinephrine concentration. Because bupivacaine is only commercially available in Canada with 1:200,000 epinephrine, our final solution contains 1:156,666 epinephrine. It is not clear whether this is sufficiently concentrated for all applications of tourniquet-free hand surgery, compared with the published data using 1:100,000 epinephrine containing lidocaine. We have performed the laboratory work on plain solutions of lidocaine and bupivacaine with freshly added epinephrine (not reported), but not the clinical work. The emphasis in the present study was to investigate commercially prepared epinephrine containing LA solutions because we believe this will appeal to the widest audience of clinicians.

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