Comparison of lidocaine CO_2, two per cent lidocaine hydrochloride and pH adjusted lidocaine hydrochloride for Caesarean section anaesthesia

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Lidocaine can be prepared in a variety of ways which may affect the characteristics of neural blockade achieved. Experimental evidence is equivocal as to the clinical impact of the use of different lidocaine preparations. A randomized, double-blind study was performed to investigate the differences in epidural anaesthesia for Caesarean section using three different lidocaine solutions: lidocaine CO_2, two per cent lidocaine and two per cent lidocaine with its pH adjusted by the addition of bicarbonate. No differences were found among the groups in time of onset of neural blockade, quality or duration of neural blockade, time to delivery of the infant or volume of anaesthetic solution injected into the epidural space. A significant difference was found between the pH's of the solutions used. It is concluded that all three solutions are equally efficacious in epidural anaesthesia for Caesarean section.

Théoriquement, on peut moduler un bloc nerveux en choisissant parmi les diverses préparations de lidocaïne disponibles. On ne sait toutefois pas si ces différences ont un impact pratique. Dans le cadre d'une étude randomisée et à double insu lors de césariennes, nous avons évalué les caractéristiques du bloc nerveux produit par la lidocaïne CO_2, la lidocaïne à deux pour cent et la lidocaïne à deux pour cent avec pH ajusté par addition de bicarbonate. Le temps de latence, la durée et la qualité du bloc, le volume d'anesthésique injecté et le temps s'écoulant jusqu'à la naissance étaient semblables d'un groupe à l'autre. Les solutions avaient cependant un pH significativement différent. Toutes ces préparations sont également efficaces pour obtenir une anesthésie épidurale appropriée à une césarienne.

Key words
ANAESTHETIC TECHNIQUES: epidural, obstetric;
ANAESTHETICS, LOCAL: lidocaine, carbonation, pH adjustment;
PREGNANCY: Caesarean section.

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Presented at the Annual Meeting of the Canadian Anaesthetists' Society, May 1988, Halifax N.S.

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Local anaesthetics are generally marketed as acidic salts, to improve solubility in water. Lidocaine is either acidified with hydrochloric acid, forming lidocaine hydrochloride, or it is carbonated. The use of lidocaine CO_2 for epidural anaesthesia has generated a great deal of controversy. Some studies have indicated that the carbonate is superior to the hydrochloride,[1–4] while others have shown that there is no difference in onset or efficacy in anaesthesia for Caesarean section between the two solutions.[5–8] There has also been a resurgence of interest in the use of alkalinized local anaesthetic, a solution with its pH raised to 7.0 or greater by the addition of a base, usually bicarbonate, shortly before the induction of anaesthesia. This has been shown in some studies to improve the efficacy of the local anaesthetic.[9,10]

A randomized, double-blind study has been conducted to compare two per cent lidocaine hydrochloride and alkalinized lidocaine and carbonated lidocaine, when used to provide epidural anaesthesia for Caesarean section.

Methods

With the approval of the Clinical Screening Committee for Research Concerning Human Subjects of the University of British Columbia, 60 patients, ASA physical status

I or II, presenting for elective Caesarean section under epidural anaesthesia, were enrolled. After giving informed consent the patients were randomized into one of three groups. Group One received lidocaine hydrochloride two per cent, Group Two received lidocaine CO_2, and Group Three received two per cent lidocaine hydrochloride with its pH increased to 7.0 or greater by the addition of two ml 8.4 per cent sodium bicarbonate to each twenty ml of lidocaine solution. Epinephrine was freshly added to each solution, to a concentration of 1/400,000.

All patients had an epidural catheter inserted either at the L_{2-3} or L_{3-4} interspace. The local anaesthetic was administered in 3 ml incremental doses rapidly injected every one to two minutes to achieve a sensory block to T_4. Both patient and observer were blinded to the local anaesthetic solution used.

Time zero was recorded as the time of injection of a three ml test dose of the local anaesthetic solution and the following variables were recorded: time to the onset of sensory loss at L_1; time to the onset of sensory loss at the S_2 dermatome (measured behind the knee); time to block at T_4; time to delivery of the infant; duration of anaesthesia (as measured by the regression of the block by two dermatomes); fentanyl supplementation used; volume of local anaesthetic administered; and the pH of the local anaesthetic solution. Sensory loss to temperature was assessed every thirty seconds, and confirmed with pinprick. Motor block was not assessed. The pH was measured after the addition of epinephrine, within ten minutes of the initial opening of the vial, using a Fisher digital pH meter.

At the end of the study, data were analyzed for statistical significance using the analysis of variance, and the Kruskal-Wallis test. Significance was defined as a $P \leq 0.05$.

Results

There was no difference among the groups as to patient height, weight, parity or volume of local anaesthetic solution (Table I). The number of patients requiring supplemental fentanyl (administered after the birth of the baby) was similar in all three groups. As shown in Table II there was no difference in the time to onset of the block at L_1 or the time to peak effect. Onset of sensory block at the S_2 dermatome was faster with lidocaine CO_2 than with the other two solutions. This difference approached but did not achieve statistical significance (Table II). There was also no difference in duration of block among the three local anaesthetic solutions (Table II). The only significant difference found in the study was among the pH's of the three solutions, a predictable result, given the design of the study (Figure).

TABLE I Patient characteristics

	Lido CO_2	*pH adj lidocaine*	*Lido 2%*
Number	20	20	20
Height (cm)	162 ± 9.6	160 ± 6.7	159 ± 6.0
Weight (kg)	72 ± 11	72 ± 11	73 ± 9
Volume of LA (ml)	17.5 ± 3.2	18.0 ± 2.6	19.2 ± 3.1
Patients requiring supplemental fentanyl (*n*)	12	9	14

All values are mean ± SD.
No significant difference.

TABLE II Results: time in minutes

	Lido CO_2	*pH Adj lidocaine*	*Lido 2%*
Onset L_1	3.8 ± 1.7	4.3 ± 2.1	4.2 ± 2.1
Onset S_2	6.8 ± 3.1	9.3 ± 3.2	10.4 ± 5.7
Peak effect	19.4 ± 10.3	18.4 ± 5.3	20.6 ± 5.7
Duration	118 ± 45	124 ± 31	114 ± 27

All values are mean ± SD.
No significant difference.

Discussion

Lidocaine is a weak base, with a pKa at 36° C of 7.61.[11] As such, it exists at physiological pH in two forms: a charged, protonated molecule, and an uncharged base. Lidocaine is marketed at a pH between 5.0 and 7.0 since aqueous solubility is higher at this range of pH than at a more physiological pH.[12] The lidocaine molecule is most effective at blocking the sodium channel when it is protonated, but it primarily gains access to the channel by diffusion through lipid membranes.[12] The uncharged base is over 4,000 times more lipid-soluble than its cationic counterpart.[11] The preponderance of charged lidocaine in the aqueous solution results in slow transfer of the lidocaine across lipid membranes and slows the onset of the block.

Methods of improving clinical efficacy of lidocaine in nerve blockade have been the subject of ongoing research and interest. Increasing the pH of the aqueous solution of lidocaine prior to use has long been recognized as one such method. Investigations into the use of pH-adjusted local anaesthetics have produced varied results in both epidural and perivascular nerve blocks. In the brachial plexus, alkalinized bupivacaine has been shown, in a randomized double-blind study, to be no more effective than the standard, commercial solution in its onset time, block quality or block duration.[13] However, in the epidural space, increasing the pH of bupivicaine from 5.49 to 7.04 significantly decreased latency and increased

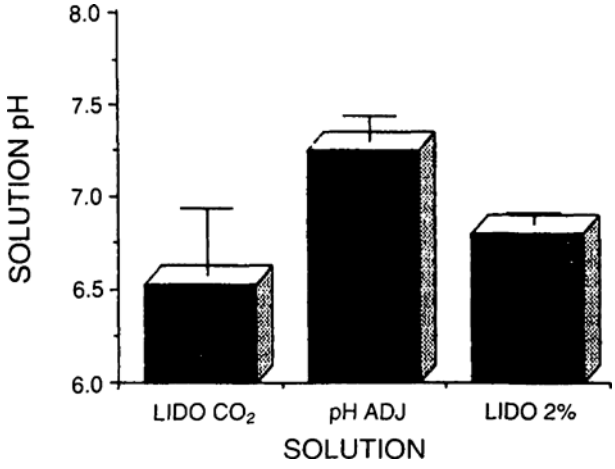

FIGURE Comparison of pH among the three solutions. Each value is the mean ± standard deviation. $P < 0.001$.

duration.[9] Similarly, alkalinized lidocaine with a pH greater than 7.0 has been reported to be faster in onset than lidocaine with a pH of less than 5.0.[10] A lidocaine solution with a pH of 6.35 was also included in the latter study but the report was unclear as to the significance of the differences between this solution and the others.

Lidocaine can also be acidified by carbonation to improve aqueous solubility. The addition of carbon dioxide rather than HCl has a number of potential effects on the pharmacology of the compound. Upon injection, the CO_2, at approximately 760 torr, diffuses rapidly away from the solution, resulting in more rapid alkalinization.[1,12] A portion of the CO_2 diffuses intracellularly, lowering the intracellular pH, and trapping a larger proportion of the lidocaine molecules in their charged, protonated form.[1,12,14] This results in an increased concentration of lidocaine in its active form for the blockade of sodium channels. In addition, CO_2 has effects that decrease axonal conduction, independent of the presence of lidocaine.[15,16]

Early work by Bromage indicated the superiority of lidocaine CO_2 over lidocine HCl, using non-blinded studies in which the local anaesthetic was injected in a single bolus.[1,2] Houle studied patients presenting for vaginal delivery under epidural anaesthesia, in a non-randomized, non-blinded format with large, repeated boluses of local anaesthetic, and showed no statistically significant difference between lidocaine CO_2 and lidocaine HCl.[4] However, the investigators felt that their results were not inconsistent with the findings of Bromage. Two randomized, double-blind studies, using the single-bolus technique, and one randomized, double-blind study using incremental injections of local anaesthetic to achieve anaesthesia, showed no significant difference in onset or height of block between the two solutions.[5–7] Martin showed improved sensory block at L_5-S_1 and Morrison found an increase in motor block with lidocaine CO_2 but these variables are not important in anaesthesia for Caesarean section. Recently, another study by Nickel and Bromage, randomized and double-blind but still using a single-injection technique, showed that lidocaine CO_2 was, again, superior to lidocaine HCl in epidural anaesthesia.[3] This contrasts with this study which showed that, except for pH, there was no difference between the three solutions when used for epidural anaesthesia for Caesarean sections.

A possible explanation for the differences among the various studies is that the lidocaine solutions used may not have had a similar pH. In reported studies in which the pH of the solutions used were specified, those that found a significant difference between lidocaine HCl and lidocaine CO_2 used lidocaine with a mean pH less than 6.5 or a range of 6.29 to 6.71.[1,3] This is lower than the pH of the lidocaine used in the current study. Also, this study used an incremental injection technique in achieving an adequate block height, while most of the studies which reported a significant difference between HCl and CO_2 solutions used a single injection of a predetermined dose. While the single-injection technique is time efficient, the possible risk of hypotension or high block makes the incremental method more desirable, particularly in the parturient. These two factors – the relatively high pH of the lidocaine solutions used in the current study and the incremental method of administration – may also account for the lack of difference that was found between alkalinized lidocaine, and the other two solutions.

We conclude that lidocaine CO_2, two per cent lidocaine HCl and alkalinized lidocaine HCl, when combined with epinephrine and administered in small, incremental doses, are similar in their effectiveness for epidural anaesthesia for Caesarean section.

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