The effect of pH adjustment of bupivacaine on onset and duration of epidural anaesthesia for Caesarean section

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Previous studies have reported that elevation of the pH of local anaesthetics results in more rapid onset of action, with enhanced quality and duration of block. This study investigated the effect of pH adjustment of 0.5 per cent bupivacaine immediately prior to epidural anaesthesia for Caesarean section. Addition of 0.1 ml of 8.4 per cent sodium bicarbonate to 20 ml of 0.5 per cent bupivacaine consistently raised the pH of the local anaesthetic from 5.49 to 7.04 (mean values). One hundred patients, presenting for elective Caesarean section under epidural anaesthesia participated in the study. Forty patients received epidural anaesthesia, using pH-adjusted 0.5 per cent bupivacaine, in a dosage adequate to produce block to the T_4 level. A control group of 40 patients received the standard commercial preparation of 0.5 per cent bupivacaine. A further ten patients in each group received epidural anaesthesia using 0.5 per cent bupivacaine with the addition of 1:400,000 epinephrine, to study the effect of epinephrine on pH adjustment of the local anaesthetic. Elevation of the pH of the local anaesthetic significantly increased the speed of onset of action from 6.4 minutes to 3.2 minutes and the time to peak effect from 24.8 minutes to 18.1 minutes, while the duration of anaesthesia was increased from 124.8 minutes to 147.3 minutes. The time to S_2 segment blockade was also shortened from 13.5 to 8.6 minutes. Addition of 1:400,000 epinephrine to the local anaesthetic did not influence the effect of pH adjustment. Maternal and umbilical cord plasma levels of bupivacaine were not affected by pH adjustment of the local anaesthetic, while MV/UV and UA/UV ratios were unaltered.

Key words
ANAESTHESIA: epidural, obstetric; LOCAL ANAESTHETICS: bupivacaine.

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Twenty years after Loder[1] reported that addition of dextran to local anaesthetics resulted in prolonged duration of intercostal nerve blocks, Rosenblatt and Fung[2] demonstrated that this effect was the result of an increase in the pH of the local anaesthetic solution. Galindo[3] later demonstrated that addition of sodium bicarbonate to bupivacaine, mepivacaine and lidocaine, to raise the pH of the solutions to 7.0 and 7.4, consistently resulted in improved quality and longer duration of epidural anaesthesia. A previous study in this institution[4] examined the effect of raising the pH of 0.25 per cent bupivacaine prior to administration of epidural analgesia during labour. A significant increase in the speed of onset and duration of analgesia was noted with this low drug concentration and 8 ml doses.

This double-blind study was undertaken as a follow-up to the earlier study,[4] to examine the effect of raising the pH of 0.5 per cent bupivacaine to > 7.0, immediately prior to its administration to produce epidural anaesthesia for Caesarean section. It was designed to demonstrate whether the increased drug concentration and larger total dose might further shorten the time of onset of the block, improve its quality and shorten the time to peak effect. The latter effect was not noted in the earlier study.

Methods

The study was approved by the Clinical Screening Committee for Research Involving Human Subjects at the University of British Columbia. Written informed consent was obtained from 100 ASA physical status class 1 patients presenting for elective Caesarean section, who were enrolled in the study. Each patient received an

intravenous infusion of 1000 to 1500 ml lactated Ringer's solution. An epidural catheter was inserted at the L_{2-3} or L_{3-4} level and threaded 2 to 3 cm cephalad, after local skin infiltration with 1 ml of 2 per cent lidocaine. The patients were randomly assigned to one of four groups:

Group 1 (n = 40) received the standard commercial preparation of 0.5 per cent bupivacaine (Marcaine®)

Group 2 (n = 40) received pH-adjusted 0.5 per cent bupivacaine

After completion of these 80 cases, a further 20 patients were added, in order to study the effect of addition of epinephrine on pH adjustment of the local anaesthetic:

Group 3 (n = 10) received the commercial preparation to which 1:400,000 epinephrine had been freshly added

Group 4 (n = 10) received the pH-adjusted solution with fresh addition of 1:400,000 epinephrine

Both the patient and the anaesthetist were blinded to the pH of the solution used. The pH of the bupivacaine was adjusted by the addition of 0.1 ml of 8.4 per cent (wt/vol) sodium bicarbonate to 20 ml of 0.5 per cent bupivacaine, immediately prior to injection into the epidural space. The bupivacaine/bicarbonate mixture was inverted, without shaking, a number of times to promote adequate mixing. No precipitate was observed in any preparation. The pH of a sample of the formulation was measured within 30 minutes of mixing, using a Fisher model 129 digital pH meter with a combination electrode with a calomel reference.

A "test dose" of 3 ml bupivacaine was injected, followed by 3 to 5 ml increments at three minute intervals, to produce anaesthesia to about the T_4 level. Because of the study protocol, epinephrine was only present in the test dose in the 20 cases in which it had been added to the study solution. Patients with failed blocks were not included in the study.

The following information was recorded:

Study population

Maternal age, height, weight, parity

Drug effect

The time of injection of the test dose was regarded as "zero" time. The time of *onset* was recorded as loss of temperature sensation (to ice) at the L_1 dermatome. Time to loss of temperature sensation in the S_2 *dermatome* was also recorded. These observations were conducted at 30 second intervals. Time to *peak effect* was recorded as the time to thermosensory loss (to ice) at the highest segment reached, with testing of the level being done prior to each incremental dose. The *duration* of the block was regarded as the time to regression by two segments, as evidenced by return of temperature sensation. The *quality* of the block was judged by the need for supplemental intravenous narcotic (fentanyl) during the surgery.

Maternal venous blood samples were drawn, for estimation of plasma bupivacaine levels, 15 minutes after "zero" time. Umbilical venous and arterial samples were obtained at the time of delivery, from doubly clamped cord segments. Because the small cord blood volumes obtained precluded determination of free bupivacaine, only total bupivacaine was measured.

Drug analysis

A modified extraction procedure of Zylber-Katz *et al.*[5] was followed to determine plasma bupivacaine (free base) levels using 0.1–0.5 ml plasma, orphenadrine (1 $\mu g \cdot kg^{-1}$) as internal standard and 0.2 ml toluene as the final extraction solvent.

A capillary gas–liquid chromatograph (Hewlett–Packard model 5830A) equipped with a nitrogen phosphorous detector and a 25 meter × 0.31 mm ID cross-length 5 per cent phenylmethyl silicone coated fused silica column was used for all analyses. The splitless injection mode was employed with a 4 μl sample being injected by an automatic liquid sampler. The modified assay method has been found to show good lincarity over the concentration range studied. Within-run precision (repeatability) of a representative calibration curve showed good reproducibility with coefficients of variability ranging from four to 12 per cent.

Statistical analysis

Data were analyzed using Student's t test and the Mann–Whitney U test to determine the significance of pH-adjustment of bupivacaine. A value of $p < 0.05$ was considered statistically significant.

Results

The patients in each of the four groups were comparable with regard to age, height, weight and parity (Table I).

The pH of the standard preparation of bupivacaine was 5.49 ± 0.86 (SEM) and that of the pH-adjusted solution was 7.04 ± 1.1 (Table II). Raising the pH of bupivacaine resulted in significant shortening of the onset time from 6.4 minutes to 3.2 minutes ($p < 0.001$), the time to block of the S2 segment from 13.5 to 8.6 minutes ($p < 0.001$) and the time to peak effect from 24.8 to 18.1 minutes ($p < 0.001$). The duration of the block was lengthened from 124.8 minutes to 147.3 minutes ($p < 0.01$). The quality of the block was not affected by pH adjustment of bupivacaine and the total dose of local anaesthetic was similar in both groups.

The addition of 1:400,000 epinephrine (Table III) did not influence the effect of pH adjustment, but did increase

TABLE I Demographic data

	Standard bupivacaine		*pH-adjusted bupivacaine*	
	plain (n = 40)	*with epinephrine (n = 10)*	*plain (n = 40)*	*with epinephrine (n = 10)*
*Age (yr)	30.1(22–39)	32.3(27–39)	32.2(23–39)	31.6(24–39)
*Height (cm)	160.3(150–175)	160 (150–170)	161.3(142–178)	162 (155–173)
*Weight (kg)	73.6(50.8–107)	73.8(57–101.6)	74.9(54.4–127.5)	76.2(65.8–93)
Parity – nulliparas	6	1	10	2
– multiparas	34	9	30	8

*Mean (range).

TABLE II Effect of pH adjustment of bupivacaine (mean ± Sem)

	Standard bupivacaine	*pH-adjusted bupivacaine*
pH	5.49 ± 0.86	7.04 ± 1.1 *
Onset time (min)	6.4 ± 0.34	3.2 ± 0.19*
S_2 onset time (min)	13.5 ± 0.82	8.6 ± 0.58*
Time to peak effect (min)	24.8 ± 1.04	18.1 ± 0.8*
Duration (min)	124.8 ± 4.86	147.3 ± 4.38†
Bupivacaine dose (mg)	97.4 ± 2.3	95.9 ± 1.96

*p = <0.001.
†p = <0.01.

TABLE III Effect of addition of 1:400,000 epinephrine on pH adjustment of bupivacaine (mean ± Sem)

	Standard bupivacaine (n = 10)	*pH-adjusted bupivacaine (n = 10)*
pH	5.53 ± 0.57	7.02 ± 0.25*
Onset time (min)	6.6 ± 0.57	3.2 ± 0.4 *
S_2 onset time (min)	13.4 ± 1.8	8.8 ± 1.1
Time to peak effect (min)	25.9 ± 2.47	18.5 ± 1.95
Duration (min)	150 ± 12.7	146 ± 10.17
Bupivacaine dose (mg)	96.5 ± 5.3	91.5 ± 4.42

*p < 0.001.

TABLE IV Plasma bupivacaine levels ($\mu g \cdot ml^{-1}$)

	Standard bupivacaine	*pH-adjusted bupivacaine*
Maternal vein*	0.595 ± 0.079(n = 25)	0.546 ± 0.068(n = 23)
Umbilical vein*	0.266 ± 0.037(n = 24)	0.224 ± 0.021(n = 22)
Umbilical artery*	0.159 ± 0.025(n = 19)	0.148 ± 0.016(n = 16)
MV/UV ratio	2.24	2.44
UA/UV ratio	0.59	0.66

*Mean ± SEM.

the duration of action of the standard bupivacaine preparation to 150 ± 12.7 minutes.

The maternal venous, umbilical venous and umbilical arterial plasma bupivacaine levels, as well as the MV/UV and UA/UV ratios (Table IV) were not significantly different between the groups.

Discussion

The addition of sodium bicarbonate to a local anaesthetic will consistently raise the pH of the solution and it has been demonstrated[3,4,6] that the rate of onset of epidural analgesia is inversely related to this pH change. Local anaesthetic solutions contain both charged cations and nonionized (uncharged) free base. In vitro studies by Ritchie *et al.*[7,8] indicated that the uncharged base penetrates the nerve sheath rapidly. After diffusion through the nerve membrane it is the positively charged cation which binds with the receptor sites in the sodium channels, thus blocking nerve conduction.

Using the Henderson–Hasselbach equation, it can be calculated that at pH 5.5, less than one per cent of the drug will be in the nonionized free base form. In this study, addition of 0.1 ml 8.4 per cent sodium bicarbonate to 20 ml 0.5 per cent bupivacaine raised the pH of the solution to a mean of 7.04 and a calculated increase in the proportion of uncharged base to greater than ten per cent.

Gros[9] and Lawen[10] in 1910, described a shortened onset time and an "increased potency" of local anaesthesia when sodium bicarbonate was added to procaine. Recent studies[3,4,6] have indicated that these effects are related to the pH change produced by the sodium bicarbonate. Similar effects have been observed when carbon dioxide is added to lidocaine hydrochloride.[11–13] Bromage *et al.*[12] suggested that rapid diffusion of carbon dioxide away from the solution, after the vial is opened, results in a rise of pH to seven, or above.

The shortened onset time and lengthened duration of epidural anaesthesia, in this study, were similar to those reported in other studies.[3,4,6] In a previous study,[4] using 0.25 per cent bupivacaine during labour, it was reported that pH adjustment of the local anaesthetic did not change the time to peak effect of the drug. This contrasted with

the shortened time to peak effect reported by Galindo[3] (using 20 ml doses of 0.5 per cent bupivacaine) and the authors suggested that this effect was probably dose-related. In the present study, the larger bupivacaine doses administered resulted in a marked shortening of this time from 24.8 minutes to 18.1 minutes (Table II), confirming the earlier suggestion. However, while the highest level of sensory blockade was reached more rapidly, after raising the pH of the local anaesthetic, there was no difference noted in the sensory level reached, nor the quality of the block. The total dose of local anaesthetic used was not significantly smaller in the pH adjusted group, which is surprising and difficult to explain.

Addition of 1:400,000 epinephrine to 0.5 per cent bupivacaine had no apparent effect, other than to lengthen the duration of action of the standard preparation from 124.8 minutes to 150.1 minutes. Lund *et al.*[14] reported that epinephrine has little effect on the duration of action of bupivacaine, while Bromage[15] stated that addition of epinephrine to bupivacaine will improve the quality of blockade. These observations are not supported by the present study.

Blood for maternal plasma bupivacaine levels was obtained at a constant time after epidural injection of bupivacaine commenced. However, the times to delivery of the babies, when cord blood specimens were obtained, varied. This difference may well have some effect on maternal:infant drug ratios. The maternal plasma levels of bupivacaine were not significantly higher after alkalinization. This observation may be related to the time the blood samples were drawn (15 minutes after "time zero"). Appleyard[16] reported that plasma bupivacaine levels rose more rapidly after epidural injection of carbonated bupivacaine than after similar doses of bupivacaine hydrochloride, in the absence of epinephrine. There was a significant difference noted up to 4 minutes after injection, but after 12 minutes the difference was not significant.

This study has demonstrated that adjustment of the pH of 0.5 per cent bupivacaine towards the physiologic range of tissue pH, prior to injection into the lumbar epidural space, will result in a more rapid onset of anaesthesia, without affecting the extent of segmental spread of the block. The S_2 segment, which is frequently difficult to block, was also anaesthetized more rapidly and the duration of anaesthesia was significantly prolonged. This study again demonstrates the advantage of pH-adjustment of 0.5 per cent bupivacaine, when this drug is used to produce epidural anaesthesia for Caesarean section.

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Résumé

Des études antérieures ont démontré que l'élévation du pH des anesthésiques locaux raccourcissait le temps de latence, améliorait la qualité et augmentait la durée du bloc. Cette étude investigue les effets d'un ajustement du pH de 0.5 pour cent de bupivacaïne immédiatement avant l'anesthésie épidurale pour une césarienne. L'addition de 0.1 ml de 8.4 pour cent de bicarbonate de soude à 20 ml de 0.5 pour cent de bupivacaïne augmentait immanquablement le pH de l'anesthésique local de 5.49 à 7.04 (valeurs moyennes). Cent patientes se présentant pour une césarienne élective sous anesthésie épidurale ont participé à cette étude. Quarante patientes ont reçu une anesthésie épidurale avec 0.5 pour cent de bupivacaïne à pH ajusté avec une dose adéquate pour produire un bloc T_4. Un groupe-contrôle de 40 patientes ont reçu la préparation commerciale standard de 0.5 pour cent de bupivacaïne. D'autre part dix patientes de chaque groupe ont reçu une anesthésie épidurale utilisant 0.5 pour cent de bupivacaïne avec l'addition de 1:400,000 d'épinéphrine afin d'étudier les effets de l'épinéphrine sur l'ajustement du pH de l'anesthésique local. L'augmentation du pH de l'anesthésique local a augmenté significativement la rapidité d'installation du bloc de 6.4 minutes à 3.2 minutes et le temps pour un effet maximal de 24.8 minutes à 18.1 minutes, alors que la durée de l'anesthésie a augmenté de 124.8 à 147.3 minutes. Le temps de blocage du segment S_2 a été aussi raccourci de 13.5 à 8.6 minutes. L'addition de 1:400,000 d'épinéphrine à l'anesthésique local n'a pas influencé l'effet de l'ajustement du pH. Les niveaux plasmatiques de bupivacaïne dans le cordon ombilical ainsi que chez la mère n'ont pas été affectés par l'ajustement du pH de l'anesthésique local alors que les rapports MV/UV et UA/UV sont demeurés inchangés.