Alkalinization of lidocaine 2% does not influence the quality of epidural anaesthesia for elective Caesarean section

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This double-blind randomized study compared the effects of an epidural injection of lidocaine hydrochloride 2% (HCl) (Group 1), alkalinized lidocaine 2% (1 ml $NaHCO_3$ per 10 ml of solution) injected either immediately (Group 2) or one hour after preparation (Group 3) in 45 parturients (n = 15 per group) scheduled for elective Caesarean section. Each patient received 16 ml of one of the three solutions. The mean pH values measured just before administration with a pH-meter PHM 64 Metrohm AG were 6.77 for the HCl lidocaine 2% solution, 7.34 for the freshly alkalinized solution and 7.35 for the solution prepared one hour before injection. The median maximal sensory level (range) observed was T_3 (T_8–C_7), T_4 (T_5–C_8) and T_4 (T_6–C_6), obtained after 19 ± 6 min, 18 ± 8 min and 16 ± 6 min respectively for each group. A motor block of grade 2 or 3 on the Bromage scale was obtained in 11, 10 and 14 patients respectively. No failure was observed although 3, 5, and 2 patients in Groups 1, 2, and 3 respectively required a supplementary bolus 20 min after the initial injection because of inadequate sensory level or pain at the operative site. In conclusion, this study shows that neither fresh alkalinization of 2% lidocaine nor the delay of one hour between preparation and injection of the alkalinized solution influences the onset or quality of epidural anaesthesia for elective Caesarean section.

Cette étude randomisée, réalisée en double-aveugle, a comparé les effets anesthésiques de la lidocaïne HCl 2%, de son alcalinisation immédiate à raison de 0,1 meq par ml, et d'un délai d'une heure entre la préparation de la solution alcalinisée et son injection, en césarienne élective sous anesthésie péridurale continue chez 45 patientes. Chaque patiente a reçu une injection péridurale de 16 ml de la solution correspondant au groupe auquel elle a été attribuée. Les pH moyens mesurés étaient 6.77 pour la lidocaïne 2% seule, 7.34 pour la solution fraîchement alcalinisée et 7.35 pour la solution alcalinisée préparée à l'avance. La valeur médiane (étendue) du niveau sensitif maximal était à D_3 (D_8–C_7), D_4 (D_5–C_8), et D_4 (D_6–C_6), obtenu après 19 ± 6 minutes, 18 ± 8 min et 16 ± 6 min pour les trois groupes respectivement. Un bloc moteur de degré 2 ou 3 selon l'échelle de Bromage a été obtenu chez 11, 10 et 14 patientes respectivement. En conclusion, les résultats de cette étude indiquent d'une part que l'alcalinisation de la lidocaïne 2%, et d'autre part qu'un délai d'une heure entre l'alcalinisation de la solution et son injection n'influencent pas les caractéristiques d'une anesthésie péridurale pour césarienne.

Key words
ANAESTHESIA: obstetrical, Caesarean section;
ANAESTHETIC TECHNIQUES: epidural;
ANAESTHETICS LOCAL: lidocaine, alkalinization.

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Epidural anaesthesia is widely performed for Caesarean section.[1,2] The literature describes several factors influencing onset, duration and quality of epidural anaesthesia in obstetrics[3] among which the most important are: dose of local anaesthetics, volume and concentration of solutions, and additives.

In 1910, Läwen[4] observed that the addition of sodium bicarbonate 0.5% to a 1% procaine solution enhanced local anaesthetic potency and reduced onset time. The proposed mechanism of action of sodium bicarbonate is an increase in the percentage of un-ionised molecules present in the local anaesthetic solution, thus facilitating their passage through biological membranes.[5,6] Clinical studies on alkalinization of local anaesthetic solutions have provided controversial results. Some authors[6-11] report a faster onset and a better quality of sensory and

motor blocks. Others[12-16] have failed to show any clinical advantages of alkalinization over a plain solution.

When reviewing the studies, the timing of alkalinization of the local anaesthetic solution is not mentioned. Although Bonhomme[17] has shown that an alkaline bupivacaine solution remains stable in solution for 24 hr, no data exist with an alkaline lidocaine solution. Our concern was to assess the stability of an alkalinized lidocaine solution using a clinical approach.

The aim of this study was to compare a plain solution of lidocaine 2% with two other identical solutions alkalinized one hour or immediately before epidural injection in patients undergoing elective Caesarean section.

Methods

After institutional approval, 45 consecutive unpremedicated female patients ASA status I or II undergoing elective Caesarean section were investigated.

In the operating room, the patients were monitored with an ECG, an automatic blood pressure cuff and a pulse-oximeter. A 17G venous catheter was inserted in a vein on the forearm and an isotonic crystalloid solution was infused at a rate of 10 ml · kg^{-1} over 30 min. Thereafter, fluid administration was tailored to haemodynamic variations and blood loss. All patients had a urinary catheter inserted.

The epidural space was punctured at the L_3–L_4 or L_2–L_3 interspace using an 18G Tuohy needle, with the patient in the left lateral position. The space was located using the loss of resistance technique. A 20G catheter was then threaded 4 cm cephalad. The patient was turned back to the supine position and a pillow placed under her right hip to minimize vena cava compression. A test-dose of 2 ml lidocaine 2% with epinephrine 1/200000 was injected first. Five minutes later another 16 ml of one of the following solutions were administered as rapidly as possible in a randomized double-blind fashion through the epidural catheter. The patients were attributed to their group by closed envelope the evening before, the solution was prepared by a nurse in an adjacent room.

Group 1: Lidocaine 2% with 1 ml normal saline added for each 10 ml of local anaesthetic.

Group 2: Lidocaine 2% with 1 mEq (=1 ml) sodium bicarbonate 8.4% for each 10 ml of local anaesthetic. The solution was prepared and injected immediately.

Group 3: Lidocaine 2% with 1 mEq (=1 ml) sodium bicarbonate 8.4% for each 10 ml of local anaesthetic. The solution was prepared one hour before injection.

If, 20 min after injection, the sensory level was below T_6 and/or motor block was less than grade 2 on the Bromage scale (0 = no motor block, 1 = patient unable to raise extended leg, 2 = patient unable to flex the knee, 3 = patient unable to move the ankle) a supplementary 4 ml bolus of the same solution was injected. If, ten minutes after this supplementary bolus, the sensory level was still below T_6, the case was considered a failure and general anaesthesia was performed. Surgery started as soon as a sensory level of T_6 was reached.

TABLE I Patient characteristics and preanaesthetic haemodynamic values (mean ± SD)

	Group 1 (n = 15)	*Group 2 (n = 15)*	*Group 3 (n = 15)*
Age (yr)	33 ± 4	31 ± 6	31 ± 5
Weight (kg)	73 ± 16	72 ± 11	74 ± 7
Height (cm)	158 ± 9	161 ± 7	164 ± 7
Pregnancy (wk)	38 ± 1	39 ± 1	38 ± 1
ASA status I/II/III	15/0/0	15/0/0	15/0/0
MAP (mmHg)	87 ± 16	92 ± 9	91 ± 4
HR (beats · min^{-1})	84 ± 5	85 ± 13	90 ± 17

MAP = mean arterial pressure, HR = heart rate, Group 1 = plain lidocaine 2%, Group 2 = freshly alkalinized lidocaine 2%, Group 3 = alkalinized lidocaine 2% prepared one hour before.

The following variables were noted every two minutes during the first 20 min after injection and then every five minutes up to 30 min after initial injection:

- Upper sensory level using the pin-prick test in the mid-axillary line, bilaterally, with a 24-gauge needle.
- Maximal degree of motor block on the Bromage scale.
- Variations in the mean arterial pressure (MAP) and heart rate (HR) until the end of surgery. If MAP decreased by >30% of the baseline value, 5 to 10 mg ephedrine, were administered *iv.* If the HR slowed to <45 bpm, 0.5 mg atropine was injected *iv.*
- Volume of fluids infused and urinary flow were noted every 30 min until the end of surgery.

The pH of each solution was determined just before administration with a pH-meter PHM 64, Metrohm AG®.

The data are expressed as mean ± SD or median (range). Groups were analysed using analysis of variance (ANOVA), the Kruskall-Wallis test or the Mann Witney U test as required. A $P < 0.05$ was considered significant.

Results

Patient characteristics are presented in Table I. No differences were noted among groups.

The mean pH of each solution was 6.77 ± 0.1 in Group 1, 7.34 ±0.03 in Group 2 and 7.35 ± 0.03 in Group 3 (NS).

The evolution of the sensory block during the 20 min after the initial epidural injection of local anaesthetic is

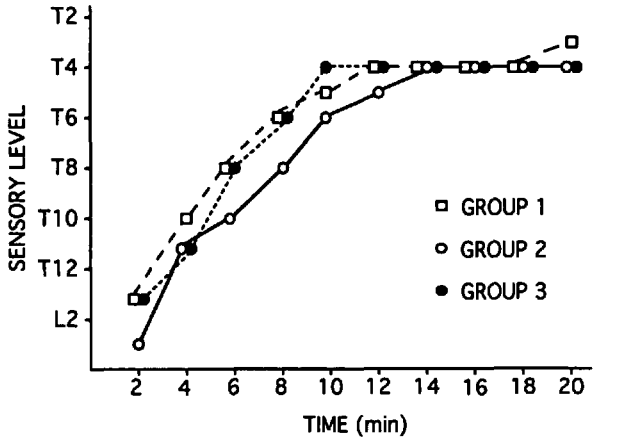

FIGURE 1 Sensory levels obtained during the first 20 min after epidural injection for the three groups, expressed as median ($n = 15$ for each group). Group 1 = plain lidocaine 2%, Group 2 = freshly alkalinized lidocaine 2%, Group 3 = alkalinized lidocaine 2% prepared one hour before.

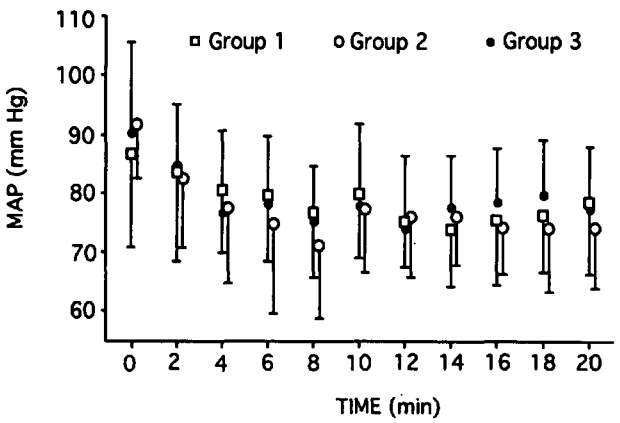

FIGURE 2 Evolution of mean arterial pressure (MAP) during the first 20 min after epidural injection for the three groups (mean ± SD, $n = 15$ for each group). Group 1 = plain lidocaine 2%, Group 2 = freshly alkalinized lidocaine 2%, Group 3 = alkalinized lidocaine 2% prepared one hour before.

TABLE II Anaesthetic characteristics during the first 30 min after epidural injection of lidocaine 2% for the three groups. Results are expressed as mean ± SD or median (range)

	Group 1 (n = 15)	*Group 2 (n = 15)*	*Group 3 (n = 15)*
Maximal sensory level	T_3 (T_8–C_7)	T_4 (T_5–C_8)	T_4 (T_6–C_6)
Obtained after (min)	19 ± 6	18 ± 8	16 ± 6
Number of patients with a motor block grade 2 or 3	11	10	14
Obtained after (min)	11 ± 13	7 ± 3	13 ± 7

Group 1 = plain lidocaine 2%, Group 2 = freshly alkalinized lidocaine 2%, Group 3 = alkalinized lidocaine 2% prepared one hour before.

TABLE III Maximal haemodynamic changes noted during the first 30 min after epidural injection for the three groups (mean ± SD)

	Group 1 (n = 15)	*Group 2 (n = 15)*	*Group 3 (n = 15)*
Maximal haemodynamic changes from baseline values for:			
- MAP (%)	−29 ± 12	−35 ± 13	−28 ± 15
- HR (%)	−10 ± 32	+6 ± 28	−12 ± 30
Onset time			
- MAP (min)	14 ± 8	13 ± 8	13 ± 8
- HR (min)	12 ± 10	18 ± 10	13 ± 7
Number of patients requiring ephedrine	6	9	8
Mean dose of ephedrine (mg)	12 ± 7	11 ± 9	12 ± 5

MAP = mean arterial pressure, HR = heart rate, Group 1 = plain lidocaine 2%, Group 2 = freshly alkalinized lidocaine 2%, Group 3 = alkalinized lidocaine 2% prepared one hour before.

shown in Figure 1. No differences were observed among groups. The median values of maximal sensory levels observed and mean onset times were comparable (Table II).

Inadequate sensory levels occurred in two patients in Group 1, three in Group 2 and one in Group 3. Furthermore, although maximal sensory levels of T_4 and T_5 were reached, one patient in Group 1, two in Group 2 and one in Group 3 required a supplementary bolus 20 min after the initial injection because of pain at the operative site. No failure was noted.

The number of patients presenting with motor block of grade 2 or 3 on the Bromage scale as well as the mean onset time of motor block were not different among groups (Table II).

Maximal variations in MAP are shown in Figure 2. The number of patients requiring ephedrine and the mean dose (mg) of ephedrine administered are shown in Table III. No differences were observed among groups. One patient in Group 1 and two patients in Group 3 needed *iv* atropine for bradycardia <45 bpm.

The duration of surgery was 49 ± 13 min in Group 1, 51 ± 8 min in Group 2 and 53 ± 18 min in Group 3 (NS). The total volumes of crystalloid infused were 1140 ± 297 ml, 1123 ± 228 ml and 1206 ± 273 ml respectively for the three groups (NS). Total urine volume was 107 ± 106 ml, 82 ± 41 ml, 61 ± 58 ml respectively for the three groups (NS). Length of hospital stay was 6.7 ± 1.5, 7.2 ± 1.4 and 6.3 ± 0.8 days respectively for each group (NS). No patient presented any complication.

Discussion

Local anaesthetics are weak bases with a pKa ranging from 7.7 to 8.9 for the commonly used drugs. Most commercial preparations are acidic to improve the stability of the solution but, at low pH, less drug is available in the undissolved active form. The relative proportion of undissociated to dissociated form is dependent on the Henderson-Hasselbach equation. Alkalinization improves the amount of local anaesthetic in the undissociated lipid soluble form, theoretically allowing a better passage through the nerve membrane, thus improving the quality and speed of surgical anaesthesia.

We found no clinical improvement of quality of anaesthesia for either alkalinized solution compared to lidocaine HCl. Several explanations can be advanced. First the lack of effect could be due to the weak pH modifications observed with alkalinization of non-epinephrine containing solutions. In a recent *in vitro* study, Berrada[15] observed that alkalinization of non-epinephrine containing local anaesthetics, whose pH values are already >6, was not useful, i.e., the increase in concentration of the ionized fraction was limited (from two to four times). However, in the same study, with alkalinization of epinephrine containing solutions of lidocaine or bupivacaine that are more acidic, the concentration of the un-ionised active fraction increased from 1000 to 3000 times.

Clinically, the results of different studies are controversial. Di Fazio *et al.*[7] noted that the onset time of sensory block was inversely proportional to the pH of a solution of lidocaine 1.5% with epinephrine injected epidurally. Other authors, while finding a quicker onset time[9] and a better quality of epidural anaesthesia using alkalinized solutions, have failed to show better results in groups where alkalinization was performed using an epinephrine-containing solution compared with non-epinephrine-containing solutions.

Using a 1:400,000 epinephrine-containing lidocaine 2% solution, Liepert *et al.*,[12] who studied patients undergoing Caesarean section, did not observe any difference in onset, spread and quality of sensory block. In his study, epinephrine was not present in the commercial acidic solution and was added after alkalinization, thus resulting probably in less pH modification. In our study, very similar to that of Liepert but using a non-epinephrine-containing lidocaine solution, pH modifications were similar to those of Liepert and no improvement in onset or quality of anaesthesia was observed.

Second, as previously noted, the methodology of the different studies cited[6–16] did not state the delay between alkalinization of local anaesthetic and its epidural injection. One explanation for the differences in the results observed in the literature is that alkalinization is always performed at the bedside with little uniformity in timing between the preparation and the epidural injection of the local anaesthetic solution. Lidocaine could then become unstable at neutral or alkaline pH values, thus being less effective if alkalinized too early.

Our study did not show any difference between the immediate preparation and the one-hour delayed preparation of alkalinized lidocaine. Thus, lack of lidocaine stability at neutral or alkaline pH cannot be retained as an explanation for the differences observed in the literature.

Finally, another reason explaining the absence of a difference between the alkalinized and the plain solutions of lidocaine is the large dose of local anaesthetic used in our study which is sufficient to speed the perineural diffusion of the local anaesthetic,[18] thus overwhelming the effect of alkalinization.

In conclusion, this study shows that neither immediate alkalinization of a lidocaine 2% solution, nor alkalinization of lidocaine 2% one hour before its epidural injection influence the spread or quality of anaesthesia for Caesarean section.

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