Effect of Increase in pH of Local Anaesthetics on Quality of Epidural Anesthesia

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Abstract

Background: The most persistent criticisms for epidural analgesia for surgery are the latency of onset and marginal intensity of sensory and motor block, so clinical trials were carried out to find out a method to decrease the latency of onset of epidural block. The present study was carried out to determine the effect of increasing pH of 2% lignocaine hydrochloride with adrenaline (1:200000) and 0.5% bupivacaine hydrochloride by addition of sodium bicarbonate administered for epidural anesthesia in inguinal herniorrhaphy. **Methods:** Eighty male patients aged 18–60 years physical status American Society of Anesthesiology I and II posted for inguinal herniorrhaphy, were enrolled in this study. After placing epidural catheter in epidural space at L3–L4, test dose of 2% lignocaine with adrenaline 3ml was given. After making patient supine, epidural dose is given with local anesthetic according to the group. Group I - 15 ml of 2% lignocaine hydrochloride with adrenaline (1:200000) +0.5 ml normal saline (pH 3.58), Group II - 15 ml of 2% lignocaine hydrochloride with adrenaline (1:200000) +0.5 ml of 7.5% (w/v) sodium bicarbonate (pH 6.78), Group III - 15 ml of 0.5% bupivacaine hydrochloride (pH 5.5) and Group IV - 15 ml of 0.5% bupivacaine hydrochloride + 0.1 ml of 7.5% (w/v) sodium bicarbonate (pH 7.5). In Groups II and IV, pH of solution was increased by addition of sodium bicarbonate. All patients were monitored for the onset of sensory and motor block, intensity of sensory and motor block, highest level of analgesia, duration of sensory and motor blockade, and effects on cardiovascular and respiratory parameters. **Results:** Onset of sensory and motor block was significantly faster in study Groups (II and IV) as compared to control Groups (I and III). Intensity of block even duration of block was significantly better in pH adjusted group. **Conclusion:** Increase in pH of local anesthetic solutions used in epidural blockade improves the quality of epidural block.

Key words: Epidural anaesthesia, local anesthetics, pH

Introduction

Epidural anesthesia increased steadily in popularity in second half of 20th century. Being a safe, simple, and effective method of regional analgesia,[1] Epidural blockade has a definite role to play in the developing countries, where the modern hospital facilities in rural areas are not very adequate. It requires minimum equipment and is necessarily more economical.

The most persistent criticisms for epidural analgesia for surgery are the latency of onset and marginal intensity of sensory and motor block.[2] Hence, clinical trials were carried out to find out a method to decrease the latency of onset of epidural block by following ways: Use of hyaluronidase, use of potassium salts, local anesthetic mixtures, and change in pH of local anesthetics.[2-5] It was observed that there was no appreciable shortening in latency of sensory block and markedly impaired quality of block with the use of hyaluronidase.[6,7] Potassium salts were not tried frequently as found to have toxic effects.[3] The local anesthetics for injection are presented as a solution of their salt usually the hydrochloride. The resulting solution is acidic. Increasing the pH of local anesthetics toward the physiological range has been reported to improve the quality of neural blockade.

The present study was undertaken to determine the effect of increasing pH of 2% lignocaine hydrochloride with adrenaline (1:200000) and 0.5% bupivacaine hydrochloride by addition of sodium bicarbonate, administered for epidural

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analgesia in inguinal herniorrhaphy. We selected both drugs for study because these two are the most commonly used drugs for epidural analgesia.

We want to study that whether addition of sodium bicarbonate to lignocaine with adrenaline and bupivacaine is beneficial and if so how much.

Methods

This prospective, randomized, double blind, controlled study was undertaken at Maharashtra Institute of Medical Sciences and Research Medical College and Yashwantrao Chavan Rural Hospital, Latur, in the Department of Anesthesiology after approval from the Institutional Ethics Committee.

We studied 80 male patients posted for inguinal herniorrhaphy. The age range was between 18 and 60 years with physical status American Society of Anesthesiology I and II.

All patients were thoroughly examined during preanesthesia evaluation including history, clinical examination, and relevant investigations were carried out. Patients with local sepsis at site of infection, coagulation disorder, sensitivity to local anesthetics, musculoskeletal disorder, vertebral deformity at lumbosacral region, and patients on anticoagulation therapy were excluded from study.

Informed written consent was taken from the patients. Patients were kept nil by mouth overnight. Pulse rate, blood pressure, and peripheral oxygen saturation (SPO_2) were recorded as base line readings before starting of procedure.

Epidural block performed with 18-G Tuohy's epidural needle in L3–L4 interspace by loss of resistance technique. Test dose of 3 ml of 2% lignocaine with adrenaline was injected followed by study drug 3 min later. Immediately after the injection, patients were placed in supine position. These eighty patients were randomly divided into 4 equal groups of twenty patients in each according to the local anesthetic administered as control group and pH adjusted group.[8-10]

Randomization was done by lottery method and anesthesiologists monitoring the patients were completely blind to the group of patient.

Group I (control group) - 15 ml of 2% lignocaine hydrochloride with adrenaline (1:200000) +0.5 ml normal saline - pH 3.58.

Group II (study group) - 15 ml of 2% Lignocaine hydrochloride with adrenaline (1:200000) +0.5 ml of 7.5% (w/v) sodabicarb - pH 6.78.

Group III (control group) - 15 ml of 0.5% Bupivacaine hydrochloride - pH 5.5.

Group IV (study group) - 15 ml of 0.5% Bupivacaine hydrochloride + 0.1 ml of 7.5% (w/v) sodabicarb - pH 7.5.

pH of the solution was measured by single Electrode Digital pH meter (systronic), manufactured by Systronic India Ltd.

All patients were monitored for the onset of sensory and motor block, intensity of sensory and motor block, highest level of analgesia, duration of sensory and motor blockade, effects on cardiovascular and respiratory parameters, and intra- and post-operative complications. Pulse rate, mean blood pressure, and SPO_2 recorded after injection of local anesthetic at interval of 5, 15, 30, 60, 90, 120, and 150 min and more than 20% change as compared to preoperative values was considered significant.

Onset of sensory analgesia

Time from administration of drug to the time required for loss of touch sensation for alcohol swab at L2 level, which was judged at 1 min interval.

Time for onset of motor block

Any subjective or objective sensation of paresis of legs.

Intensity of sensory block

Good-no supplementation, fair-intravenous (IV) sedation with midazolam and fentanyl, poor-IV midazolam, fentanyl, propofol, and laryngeal mask airway. Anesthesia maintained with O_2, N_2O, and isoflurane.

Intensities of motor block-noted as per Bromage scale are as follows:. Grade 0 - no paralysis, Grade 1 - inability to raise extended knees, Grade 2 - inability to flex knee, Grade 3 - inability to flex ankle joint.

Highest level of analgesia was checked by pinprick method and total number of segments blocked were calculated accordingly.

Duration of motor block-time from the administration of drug to the time for regaining of movements of great toe.

Duration of sensory block-time from administration of drug to regression of pinprick sensation two segments below the highest dermatome level.

All cases completed in stipulated time. Data were collected, compiled, and tabulated. All results were expressed as mean ± standard deviation. Unpaired *t*-test and Chi-square test were applied for the interpretation of results. Statistical analysis was done using statistical software primer of biostatistics. $P < 0.05$ was considered statistically significant and $P < 0.01$ - highly significant.

Using these statistical methods, comparison was done between Group I and Group II to judge effect of pH adjustment on 2% lignocaine hydrochloride with adrenaline. Similarly, Group III and Group IV compared for effect of pH adjustment of bupivacaine hydrochloride. Lignocaine and bupivacaine groups compared separately and not every group with all other groups because these two are totally different drugs in all respects (such as onset, duration, protein binding etc.).

Results

In all age groups, mean age, height, and weight of patients were comparable [Table 1].

Onset of sensory block was significantly quicker in pH adjusted Groups II (6.25 ± 1.25 min) and IV (6.90 ± 1.25 min) as compared to their respective control Groups I (10.15 ± 1.9 min) and III (11.9 ± 1.8 min). Onset of motor block was significantly quicker in pH adjusted Groups II (7.55 ± 1.68 min) and IV (8.45 ± 1.71 min) as compared to their respective control Groups I (12.4 ± 1.82 min) and III (14.05 ± 1.39 min). When onset of sensory block compared between Group I with Group II and Group III with Group IV using *t*-test $P = 0.000$, which means difference is highly significant [Graph 1].

Changes in intraoperative heart rate and mean blood pressure in the entire four groups were comparable and clinically as well statistically not significant [Graphs 2 and 3].

Duration of sensory block was significantly prolonged in pH adjusted Groups II (98 ± 13) and IV (137 ± 11.11) as compared to their respective control Groups I (90.25 ± 8.88) and III (125.5 ± 18.8). When Groups I and II were compared statistically for duration of sensory block $P = 0.029$. Similarly, when we compared Groups III and IV statistically for the duration of sensory block $P = 0.024$ [Graph 4].

Intensity of sensory and motor block was significantly more in pH adjusted Groups (II and IV) [Tables 2 and 3].

Mean number of spinal segments blocked were comparable in all groups [Table 4].

Intra- and post-operative complications were negligible in all the groups [Table 5].

Discussion

The pH of a commercially available local anesthetic solution has to be acidic to maximize stability in solution and shelf-life. The reasons include: (a) solubility – local anesthetic solutions are aqueous solutions and if provided at a pH close to 7.4, the lipid soluble uncharged form could precipitate out due to its lower water solubility. (b) Stability – the uncharged base form is more unstable at physiological pH, so degradation is minimized at a low pH where the drug is predominantly in the charged form. (c) Stability of adrenaline – the adrenaline added to some local anesthetic solutions is unstable at the physiological pH and more stable at an acidic pH.[8,11]

Alkali can be added to a local anesthetic solution immediately before injection to raise the pH. This is called "alkalinization" of the solution. Anesthetic activity is dependent on having both the ionized and nonionized forms of the drug present after injection. Alkalinization increases the proportion of nonionized drug and this could be advantageous. Care must be taken, because if too much alkali is added, the local anesthetic will precipitate. Local anesthetics are the basic drugs which have a pKa (dissociation constant) close to the normal extracellular pH of 7.4, for example lignocaine has a pKa of 7.9. The drugs exist in two forms in the solution – the uncharged basic form (B) and the charged form (BH+). B + H+ ↔ BH+. The importance of the pKa-pH relationship is that this knowledge allows the calculation of the relative amounts of these two forms. When the pH is equal to the drug's pKa, 50% of the drug is in the uncharged form, and 50% is in the charged form. In acidic solutions most of the drug will be in the charged form. When injected, the local anesthetic solution must be present in the tissues in both forms. The reason is that the drug has to diffuse to the site of action across several tissue

Table 1: Demographic data

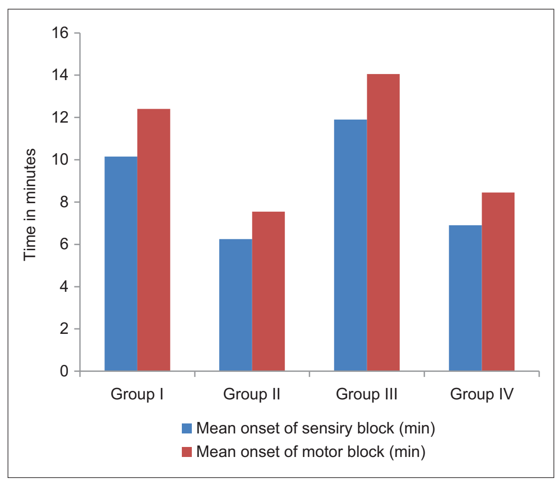
Variable	Group			
	I	II	III	IV
Mean age (years)	43.25±9.25	42±9.4	42±9.25	43±9
Mean height (cm)	159±5.02	158±4.97	159±4.75	158±4.61
Mean weight (kg)	56.5±4.13	55.75±5.19	57.15±6	56.4±4.62

Table 2: Intensity of sensory block

Intensity of sensory block	Group			
	I (%)	II (%)	III (%)	IV (%)
Good (no supplementation)	6 (30)	16 (80)	5 (25)	13 (65)
Fair (intravenous sedation)	10 (50)	3 (15)	12 (60)	2 (10)
Poor (laryngeal mask airway insertion)	4 (20)	1 (5)	3 (15)	2 (10)
Total	20 (100)	20 (100)	20 (100)	20 (100)
P	<0.05		<0.05	
Significance	Significant		Significant	

Table 3: Intensity (degree) of motor block

Intensity of motor block	Group			
	I (%)	II (%)	III (%)	IV (%)
0	-	-	-	-
I	2 (10)	-	2 (10)	-
II	10 (50)	4 (20)	15 (75)	6 (30)
III	8 (40)	16 (80)	3 (15)	14 (70)
Total	20 (100)	20 (100)	20 (100)	20 (100)
P	<0.001		<0.001	
Significance	Highly significant		Highly significant	



Graph 1: Mean onset of sensory and motor block

Table 4: Number of spinal segments blocked

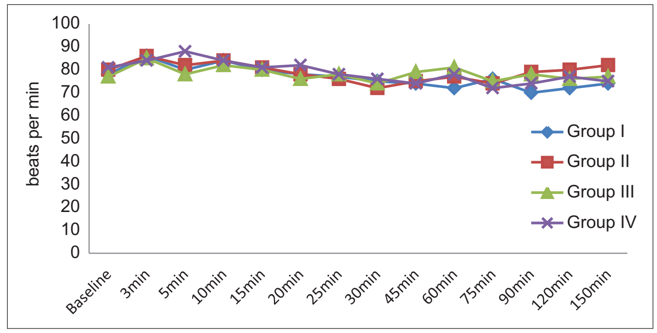
	Group			
	I	II	III	IV
Mean number of segments blocked	14.7±1.82	14.3±1.3	14.2±0.87	14±1.26
P	0.425		0.527	
Significance	Nonsignificant		Nonsignificant	

Table 5: Intra- and post-operative complications

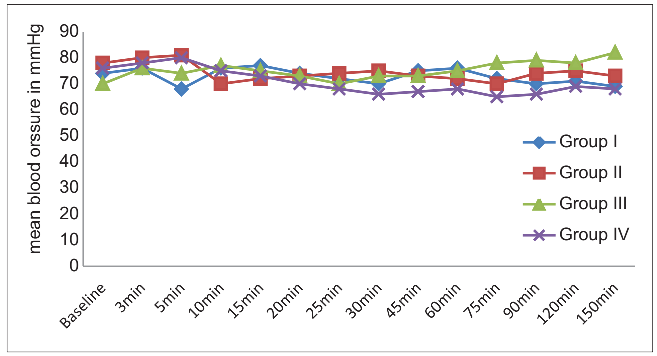
Complications	Group			
	I (%)	II (%)	III (%)	IV (%)
Bradycardia	-	-	-	-
Hypotension	-	1 (5)	-	1 (5)
Nausea/vomiting	2 (10)	1 (5)		1 (5)
Respiratory depression	-	-	-	
Sedation/drowsiness	-	-	-	-
Inadequate block	1 (5)	-	2 (10)	-
Headache/backache	1 (5)	-	-	-
Retention of urine	-	-	-	-
Neurological sequale	-	-	-	-

barriers. The uncharged lipid-soluble form will diffuse across lipid barriers, for example, perineural sheath, or cell membrane. The charged water soluble form will diffuse across tissue fluid barriers, for example interstitial fluid. The site of action of the local anesthetic molecule is the inner (or cytoplasmic) end of the sodium channel in the cell membrane. The final pathway for all injected local anesthetics is to diffuse to the cell membrane (in the charged form) then re-equilibrate to form both charged and uncharged forms adjacent to the outside of the nerve cell membrane. The molecules diffuse across the nerve cell membrane in the uncharged form then re-equilibrate in the cytoplasm to have both forms present again. Next the charged form diffuses to and binds to its "receptor" on the inside of the transmembrane sodium channel. This binding results in a conformational change in the channel protein to block the passage of sodium ions into the cell in response to a subsequent action potential.[8,11-22]

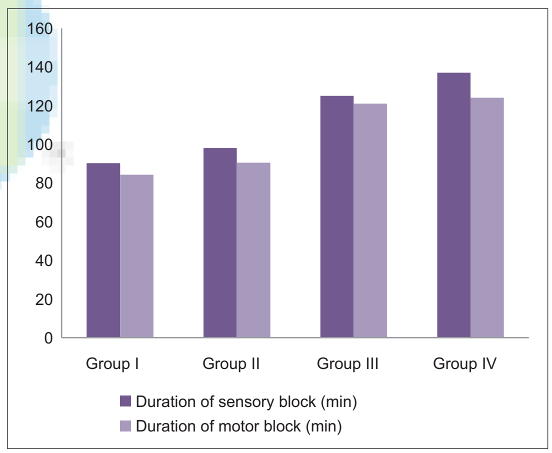
Onset of sensory block was significantly quicker in pH adjusted Group II and IV as compared to their control Group I and III. Our observation was similar to observation by many authors.[5,11,15,16,18-21,23] Addition of bicarbonate for increasing pH of local anesthetic in epidural blockade affects in two ways: (1) due to increase in pH there is rise in Uncharged base available for penetration (2) CO_2 is released and diffuses more rapidly to the interior of cell than the local anesthetics and within the axon it lowers pH thereby increasing the ionization of local anesthetics causing 2-fold effect (a) concentration of base is reduced, so increasing its gradient for diffusion into the cell (diffusion trapping), (b) CO_2 itself having nerve blocking effect either through exoplasmic free calcium or through chemical combination of channel molecules as carbonate. Onset of motor block was significantly quicker in pH adjusted group as compared to their respective control group. Onset of



Graph 2: Intraoperative changes in mean pulse rate



Graph 3: Intraoperative changes in mean blood pressure



Graph 4: Duration of sensory and motor block

sensory block was quicker than motor block as motor nerves are comparatively of large diameter than sensory and local anesthetic penetrates easily through small diameter nerves than large nerve. Intensity of sensory and motor block was found to be improved in pH adjusted group. Bicarbonate increase ionized fraction inside the nerve by diffusion trapping and this explain improvement in intensity of pH adjusted group. Our result is similar to Gosteli *et al*., Mehta *et al*., and Quinlan *et al*.[1,11,12]

Total numbers of segments blocked were similar in all the groups which suggest that spread of local anesthetic is not affected by the addition of sodabicarb. Our result coincides with Martin, Difazio, and Bromage. Prolonged duration of sensory and motor blockade in study groups can be explained on the basis of ion trapping of local anesthetic drug by diffusion trapping effect of bicarbonate. These results were similar to the studies by Gosteli *et al*., Mishra and Pandey, Mehta *et al*., and Gormley *et al*.[1,11,19,23] Cardiovascular stability is found in all groups which is the feature of epidural analgesia.[22] The incidence of postoperative complications was negligible in all groups of our study.

Conclusion

pH adjustment of local anesthetic solution used in epidural blockade definitely improves the quality of epidural block in all respects with special advantage of early onset of sensory and motor block, adequate level of analgesia, and considerable prolongation of duration of block.

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Conflicts of interest

There are no conflicts of interest.

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