

Local Anesthetic Agents for Vitreoretinal Surgery

No Advantage to Mixing Solutions

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Purpose: To compare the efficacy of lidocaine, bupivacaine, and a mixture of both in patients undergoing peribulbar anesthesia for vitreoretinal surgery.

Design: Cross-sectional study.

Participants: Ninety patients.

Methods: Patients who underwent vitreoretinal surgery were randomized into 3 groups based on the peribulbar injection they received: lidocaine, bupivacaine, or a combination of lidocaine and bupivacaine.

Main Outcome Measures: Time of onset of analgesia, akinesia, and intraoperative pain, if any, was noted. The efficacy of the block was graded from 0 to 5 depending on the adequacy of anesthesia and akinesia and the need for local supplementation.

Results: Mean times of onset (\pm standard deviation) of sensory blockade for the lidocaine, bupivacaine, and combination groups were 2.14 ± 0.18 , 2.19 ± 0.13 , and 2.17 ± 0.11 minutes, respectively ($P = 0.103$). Mean times of onset (\pm standard deviation) of motor blockade for the lidocaine, bupivacaine, and combination groups were 3.04 ± 1.81 , 4.04 ± 2.68 , and 3.38 ± 2.48 minutes, respectively ($P = 0.255$). Mean time of onset of intraoperative pain for the bupivacaine group, 149.33 ± 46.33 minutes, was prolonged significantly compared with that of the combination group, 115.83 ± 34.49 minutes, and that of the lidocaine group, 94.17 ± 49.86 minutes ($P < 0.001$). Adequate anesthesia and akinesia (grade 5) were achieved in 56.7% of the patients in the bupivacaine group compared with 23.3% in the lidocaine group and 30% in the combination group ($P = 0.049$).

Conclusions: In peribulbar anesthesia, 0.5% bupivacaine solution provides better quality of anesthesia than does combination 2% lidocaine and 0.5% bupivacaine in patients undergoing vitreoretinal surgery. *Ophthalmology* 2015;122:1030-1033 © 2015 by the American Academy of Ophthalmology.

A typical peribulbar anesthetic agent used in vitreoretinal surgery must combine the qualities of rapid onset and adequate duration of action to permit optimum surgical time while not prolonging akinesia.^{1,2} Although it is generally believed that bupivacaine has the advantage of long duration of action, it takes longer for onset of anesthesia when used in isolation; however, when it is used in combination with lignocaine, it results in the dual advantage of hastening onset time while retaining the desirable longer action duration.³ An equal amount of lidocaine and bupivacaine, although used extensively when administering peribulbar anesthesia, has no experimental basis, and it is possible that combining these agents actually could result in reduction of the effectiveness of both these anesthetics agents.⁴ Bupivacaine tends to dilute more when mixed with lidocaine than when it is combined with hyaluronidase.⁴ In the case of podiatric surgery, infiltration anesthetic used as a mixture of lidocaine and bupivacaine has been found to have no specific clinical advantage in comparison with their independent use both in terms of onset time and duration of anesthetic effect.⁵ In the case of epidural anesthesia, a combination of 2% plain lidocaine and 0.5% bupivacaine in equal amounts does

help in rapid onset, but this advantage is neutralized by early termination of action when compared with administering plain bupivacaine 0.5% separately.³ In peribulbar anesthesia, there are limited authentic clinical reports about the onset and duration of action of these mixtures compared with independent use of the drug.

With this background knowledge, the present study aimed to analyze objectively and determine whether there are any clinical advantages in terms of onset of effect or duration of action when lidocaine and bupivacaine are used in combination compared with when they are used separately in patients undergoing peribulbar anesthesia for vitreoretinal surgery.

Methods

After obtaining ethical approval from the institutional review board of the Vision Research Foundation, Chennai, India, 90 patients gave written informed consent for this study. Both men and women 40 years of age and older who were scheduled for vitreoretinal surgery (scleral buckle alone or vitrectomy plus belt buckle [240 band] with or without an additional procedure) under peribulbar anesthesia were enrolled in the study. Intellectually disabled

patients and patients with a history of intraocular surgery, orbital surgery, or ocular trauma were excluded.

All eligible patients were randomized to 1 of 3 groups to receive peribulbar injection from any 1 of the following solutions: 10 ml 2% lidocaine and hyaluronidase 15 IU/ml (lidocaine group); 10 ml 0.5% bupivacaine solution and hyaluronidase 15 IU/ml (bupivacaine group); or 5 ml 2% lidocaine solution, 5 ml 0.5% bupivacaine, and hyaluronidase 15 IU/ml (combination group). Randomization was performed based on a computer-generated random table. The anesthetic solution lidocaine (Xylocaine 2%; AstraZeneca, Bangalore, India), bupivacaine (Sensorcaine 0.5%; AstraZeneca), and hyaluronidase (Hynidase; Shreya Life Sciences, Aurangabad, India) was prepared by an anesthetist (V.V.J.). Routine monitoring for all patients included electrocardiography, noninvasive blood pressure monitoring, and pulse oximetry. An intravenous cannula was started and the fact that the procedure involved a peribulbar block was explained clearly to the patients. To maintain the uniformity of the technique, peribulbar block was administered by a single anesthetist with substantial experience in regional anesthesia for ophthalmic surgery who was blinded for the choice of anesthetics.

A 23-gauge 1-inch blunt steel needle was inserted at the inferotemporal quadrant, as far laterally as possible below the lateral rectus muscle. The needle was directed along the orbital floor, with the bevel facing the globe. It then was advanced for a distance of approximately 25 mm to the equator of the globe, where the anesthetic solution was injected, outside the muscle cone at a rate of 5 ml in 10 seconds.⁶ After negative aspiration for blood, 4 to 5 ml local anaesthetic agent was injected. Injection of the local anesthetic was stopped when there was either firmness in the globe or any resistance felt when depressing the plunger of the syringe further. After injection at the inferotemporal quadrant, the globe was massaged with the middle 3 fingers placed over a sterile gauze pad. Gentle pressure was applied using the middle finger placed directly over the eyeball for 2 minutes. For every 30 seconds, pressure was released for 5 seconds to allow for vascular pulsations to occur. At the end of the second minute, a medial peribulbar block was administered using a 26-gauge 0.5-inch disposable needle. With the bevel facing the medial orbital wall, the needle was passed into the blind pit, between the medial caruncle and canthus. It was passed backward in the transverse plane, directed at a 5° angle away from the sagittal plane and toward the medial orbital wall. If the medial wall was contacted, the tip was withdrawn slightly and the needle was redirected to a depth of 15 to 20 mm, and after negative aspiration for blood, 3 to 4 ml local anaesthetic solution was injected.⁷ Injection of the local anesthetic was stopped when there was either firmness in the globe or any resistance felt to depressing the plunger of the syringe further. Digital compression of the globe was performed again as described previously.

After administration of the second injection, the efficacy of the block was evaluated every 30 seconds. Analgesic onset was assessed by holding both the perilimbal and peripheral conjunctiva with toothed forceps, and adequacy of akinesia was assessed using the scoring system described by Brahma et al.⁸ Full movements were graded as 3, moderate movement as 2, flicker movement as 1, and no movement as 0. Ocular movements were scored for each direction of gaze in the superior, inferior, medial, and lateral directions, with a possible total maximum score of 12 points.

After a lapse of 5 minutes from the time of administering the medial injection, if the total ocular movement score was 6 or more or full movement in any one direction, then, depending on the quadrant, supplementary injection either at the inferolateral quadrant or medial peribulbar site using 3 to 5 ml of the test solution

was given. If, after another 5 minutes, the block was still inadequate, then either inferolateral or medial injection was administered again.

Vital signs were monitored throughout the surgery every 15 minutes. Patients were encouraged to communicate with the surgeon regarding onset of pain, if any, experienced during or after surgery. Time of onset of pain was recorded. If pain occurred during surgery, parbulbar supplementation with the same test solution was given by the surgeon, who also was blinded to the medication given. We included only cases in which the conjunctiva was incised and the peribulbar space exposed (i.e., the cases that had a no. 240 encircling band) so that there was always an immediate safe available option of abolishing the pain perceived by the patient by means of supplementation. After surgery, the surgeon graded the efficacy of anesthesia as shown in Table 1.^{9,10} A 1-g paracetamol tablet was given orally in the immediate postoperative period for all patients. If the pain experienced by patients in the postoperative period was moderate to severe, then 30 mg ketorolac was administered intramuscularly.

Statistical Analysis

For statistical analysis of demographic data, Student *t* test for continuous variables and the chi-square test for categorical variables were used. A 1-way analysis of variance for comparison of means between groups and the Dunnett *t* test for multiple comparisons were applied. Results were considered significant if the *P* value was less than 0.05. SPSS software version 13 (SPSS, Inc./IBM, Chicago, IL) was used for statistical analysis.

The results of a previous pilot study with 10 patients per group were taken into account and the required study size was calculated. The aim was to detect a significant difference in the time of onset of pain after peribulbar block between the bupivacaine and combination groups, accepting a 2-tailed α error of 0.05 and power of study of 80%.

Results

The groups were similar in age, gender, body weight, surgical procedure done, and duration of operation (Table 2). Figure 1 displays the time of onset of anesthesia and intraoperative pain among the groups, and Figure 2 shows the distribution of need for supplemental anesthesia or pain control in the groups. The pain started at a mean \pm standard deviation of 149.33 \pm 46.33 minutes in the bupivacaine group, 115.83 \pm 34.49 minutes in the combination group, and 94.17 \pm 49.86 minutes in the lidocaine group (*P* < 0.001). The mean times of onset of sensory blockade for the lidocaine, bupivacaine, and combination groups were 2.14 \pm 0.18, 2.19 \pm 0.13, and 2.17 \pm 0.11 minutes, respectively (*P* = 0.103). The mean \pm standard deviation times of onset of

Table 1. Grading of Efficacy of Regional Anesthesia

Grade	Efficacy of Anesthesia
5	Adequate anesthesia and akinesia throughout surgery without supplementation
4	Adequate anesthesia, inadequate akinesia, no supplementation
3	Inadequate anesthesia, adequate akinesia, supplementation required
2	Inadequate akinesia, adequate anesthesia, supplementation required
1	Inadequate akinesia and anesthesia, supplementation required
0	Inadequate anesthesia or akinesia or any other complication, necessitating termination of the operative procedure, despite supplementation

Table 2. Baseline Characteristics of the Groups

	Lidocaine Group (n = 30)	Bupivacaine Group (n = 30)	Combination Group (n = 30)	P Value
Age (yrs)	60.17±11.26	57.70±10.43	58.57±9.16	0.645
Gender (male/female)	21/9	19/11	22/8	0.696
Body weight (kg)	63.20±12.54	65.30±14.27	65.93±14.60	0.726
Surgical procedure, no.				
Scleral buckle	4	6	7	
Scleral buckle (no. 240 band) with vitrectomy	26	24	23	
Duration (min)	186.83±34.23	180.17±40.74	180.18±59.31	0.811

motor blockade for the lidocaine, bupivacaine, and combination groups were 3.04±1.81, 4.04±2.68, and 3.38±2.48 minutes, respectively ($P = 0.255$). During surgery, 10 patients (33.33%) in the bupivacaine group and 19 patients (63.33%) each in the lidocaine and combination groups required paravulbar supplementation once ($P = 0.026$). In the postoperative period, 7 patients (23.33%) in the bupivacaine group, 19 patients (63.33%) in the lidocaine group, and 15 patients (50%) in the combination group, needed intramuscular ketorolac for pain relief ($P = 0.007$). A significant number of patients attained grade 5 block in the bupivacaine group (56.67%) compared with the lidocaine group (23.33%) and the combination group (30%; $P = 0.049$; Fig 3).

Discussion

Lidocaine and bupivacaine are amide local anaesthetics, with a pKa value of 7.86 and 8.05, respectively. In ophthalmic regional anesthesia, bupivacaine is mixed with lidocaine based on the theoretical belief that this mixture acts quickly and has a longer duration of action. The rate of onset of a local anesthetic is determined largely by its pKa value, that is, the pH at which 50% of the drug exists in its active, nonionized form. It is the nonionized form of the drug that diffuses through the tissue barriers and helps achieve a rapid onset of action. Local anesthetics are weak bases, and thus when injected, those with a pKa near physiologic pH (approximately 7.0) will be less ionized than those with a higher pKa. Thus, solutions with lower pKa constants will diffuse more readily through the tissues and neuronal membranes, providing a more rapid onset. In our study, after peribulbar block, we found the onset of analgesia in all 3 groups was

approximately 2 minutes. The onset of akinesia in the lidocaine and combination groups was approximately 3 minutes, whereas that in the in the bupivacaine group was approximately 4 minutes. We found no significant difference in the time of onset of both analgesia ($P = 0.103$) and akinesia ($P = 0.255$) among the 3 groups. Similar findings were observed in infiltration anesthesia used for podiatric surgery. Gioia et al,¹¹ in their study of peribulbar anesthesia for vitreoretinal surgery, found the time of onset of analgesia and akinesia to be 5±1 and 8±5 minutes in the combination group and 5±2 and 10±5 minutes in the ropivacaine group, respectively. Both the sensory as well as the motor block were assessed by them at 5, 10, and 15 minutes after administration of injection. Our study was designed it such a way that the block was assessed for every 30 seconds after administration of the medial injection.

The site of action (Na⁺ channel) is primarily protein in the lipid environment. The more tightly the local anesthetic binds to the protein, the longer the duration of action. Bupivacaine, whose plasma binding capacity is 84% to 95%, possesses a longer duration of action compared with lidocaine, whose plasma binding capacity is 64%. During surgery, because of onset of pain, a significant number of patients in the lidocaine group (63.33%) and the combination group (63.33%) required paravulbar supplementation once compared with the bupivacaine group (33.33%; $P = 0.026$). The mean ± standard deviation time of onset of pain in the bupivacaine group, 149.33±46.33 minutes, was prolonged significantly compared with that in the lidocaine group, 94.17±49.86 minutes, and the combination group, 115.83±34.49 minutes ($P = 0.000$). A statistically significant difference was not

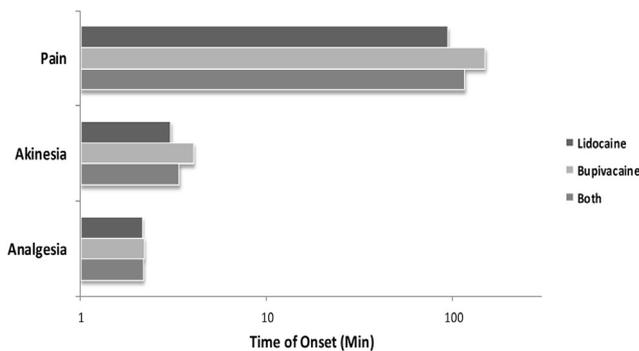


Figure 1. Bar graph showing the distribution of time of onset of akinesia, analgesia, and intraoperative pain among the groups.

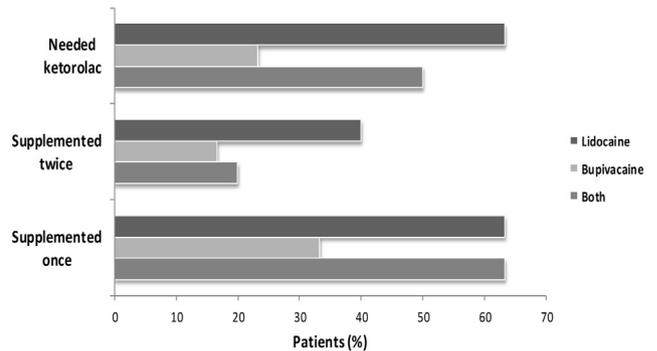


Figure 2. Bar graph showing the distribution of need for supplemental anesthesia or pain control in the groups.

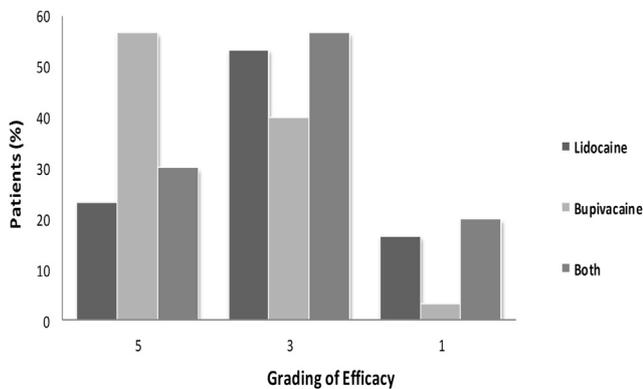


Figure 3. Bar graph showing the distribution of 1, 3, and 5 grades of block among the groups. No patient belonged to grades 0, 2, or 4.

obtained for mean duration of action between lidocaine alone and the combination groups ($P = 0.180$).

In the postoperative period, a significant number of patients attained grade 5 block in the bupivacaine group ($n = 17$, 56.67%) compared with the lidocaine group ($n = 7$, 23.33%) and the combination group ($n = 9$, 30%; $P = 0.049$; Fig 3). Throughout surgery, 17 patients (56.67%) in the bupivacaine group had adequate analgesia and akinesia, and they did not require any paravulbar supplementation (grade 5). Sixteen patients (53.33%) in the lidocaine group and 17 patients (56.67%) in the combination group required paravulbar supplementation because of inadequate analgesia (grade 3), whereas 5 patients (16.67%) in the lidocaine group and 6 patients (20%) in the combination group required paravulbar supplementation because of both inadequate analgesia and akinesia (grade 1; $P = 0.049$).

As occurred in our study, time of onset of pain occurred early in the combination group compared with the bupivacaine alone group, both in epidural as well as in infiltration anesthesia.^{3,5} Mixing 2% of lidocaine with 0.5% of bupivacaine solution in a 1:1 ratio dilutes the anesthetic mixture to 1% lidocaine and 0.25% bupivacaine, resulting in a possible reduction in efficacy of both anaesthetics.¹² Because both are amide local anesthetic solutions, they compete for the same receptors when used simultaneously, and so exhibit a shorter duration of action with a more rapid onset of action.

As a postoperative practice, we cover the operated eyes with a sterile gauze pad for 24 hours for all patients undergoing vitreoretinal surgery at our institution. We did not want to make an exception for the surgeries where the

effect of the anesthesia was being observed. This practice did pose a minor limitation to the study to the extent that the exact time of termination of the motor blockade of all the patients could not be ascertained.

From our study, we conclude that 0.5% bupivacaine is a better choice of local anaesthetic solution for patients undergoing primary vitreoretinal surgery because it produces a better quality of anesthesia and improves intraoperative and postoperative patient comfort compared with lidocaine and the combination of lidocaine and bupivacaine.

References

1. Dopfner UR, Maloney DG, Gaynor PA, et al. Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia. *Br J Anaesth* 1996;76:77–80.
2. McLure HA, Rubin AP, Westcott M, Henderson H. A comparison of 1% ropivacaine with a mixture of 0.75% bupivacaine and 2% lignocaine for peribulbar anaesthesia. *Anaesthesia* 1999;54:1178–82.
3. Zand F, Razavizadeh MR, Azemati S. Comparative study of onset and duration of action of 0.5% bupivacaine and a mixture of 0.5% bupivacaine and 2% lidocaine for epidural anaesthesia. *Acta Medica Iranica* 2004;42:256–8.
4. Chin GN, Almquist HT. Bupivacaine and lidocaine retrobulbar anaesthesia. A double-blind clinical study. *Ophthalmology* 1983;90:369–72.
5. Ribotsky BM, Berkowitz KD, Montague JR. Local anesthetics. Is there an advantage to mixing solutions? *J Am Podiatr Med Assoc* 1996;86:487–91.
6. Wong DH. Regional anaesthesia for intraocular surgery. *Can J Anaesth* 1993;40:635–57.
7. Kumar CM, Dodds C. Ophthalmic regional block. *Ann Acad Med Singapore* 2006;35:158–67.
8. Brahma AK, Pemberton CJ, Ayeko M, Morgan LH. Single medial injection peribulbar anaesthesia using prilocaine. *Anaesthesia* 1994;49:1003–5.
9. Sharma T, Gopal L, Parikh S, et al. Paravulbar anaesthesia for primary vitreoretinal surgery. *Ophthalmology* 1997;104:425–8.
10. Sharma T, Gopal L, Shanmugam MP, et al. Comparison of pH-adjusted bupivacaine with a mixture of non-Ph-adjusted bupivacaine and lignocaine in primary vitreoretinal surgery. *Retina* 2002;22:202–7.
11. Gioia L, Prandi E, Codenotti M, et al. Peribulbar anesthesia with either 0.75% ropivacaine or a 2% lidocaine and 0.5% bupivacaine mixture for vitreoretinal surgery: a double-blinded study. *Anesth Analg* 1999;89:739–42.
12. Sharma T, Gopal L, Parikh S, et al. pH-adjusted periorbital anaesthesia for primary vitreoretinal surgery. *Indian J Ophthalmol* 1999;47:223–7.

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