Clinical Ophthalmology

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ORIGINAL RESEARCH

Efficacy and safety of 0.5% levobupivacaine versus 0.5% bupivacaine for peribulbar anesthesia

This article was published in the following Dove Press journal:
Clinical Ophthalmology
20 May 2013
Number of times this article has been viewed

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Background: This randomized double-blind study examined the use of a new anesthetic agent, levobupivacaine 0.5%, which is the S(−)-enantiomer of a racemic mixture of bupivacaine, for peribulbar anesthesia and compared it with racemic bupivacaine 0.5% alone or in combination with hyaluronidase 10 IU/mL.

Methods: A total of 160 patients undergoing ophthalmic surgery were randomized into four groups (n = 40 each) to receive inferotemporal peribulbar injection of levobupivacaine 0.5% (group L), racemic bupivacaine 0.5% (group B), levobupivacaine + hyaluronidase 10 IU/mL (group LH), or racemic bupivacaine + hyaluronidase 10 IU/mL (group BH) by two anesthetists and two ophthalmologists in a ratio of 25% each. Ocular akinesia and orbicularis oculi function were evaluated using a three-point scale; a value < 5 points was considered as requiring surgery, and movements were re-evaluated the day following surgery to confirm regression of the block.

Results: The time to onset (12 ± 2.6 minutes versus 13 ± 2.8 minutes) and duration of anesthesia (185 ± 33.2 minutes versus 188 ± 35.7 minutes) were similar between groups L and B. Complete akinesia (score 0) was obtained more frequently when hyaluronidase was used in addition to the anesthetic, with occurrences of 72.5% versus 57.5% in group LH versus L, respectively, and 67.5% versus 45% in group BH versus B. Moderate hypotension (<30% of baseline) was observed in four patients (10%) in group L, two (5.0%) in group B, one (2.5%) in group LH, and three (7.5%) in group BH. The time to onset was significantly different between groups L and BH, B and BH, and LH and BH, and the duration of anesthesia differed significantly between groups B and LH, B and BH, and L and LH. The akinesia score differed significantly between groups L and LH and between groups B and LH ($P = 0.043$ and $P = 0.018$, respectively), and the number of patients with a score of 0 differed significantly between groups B and LH and between groups B and BH ($P = 0.004$ and $P = 0.017$, respectively).

Conclusion: Levobupivacaine is a long-lasting local anesthetic with limited cardiotoxicity and neurotoxicity, and may be considered the landmark for vitreoretinal surgery in elderly patients.

Keywords: bupivacaine, levobupivacaine, ophthalmic surgery, peribulbar block, regional anesthesia

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Introduction

Currently, ophthalmic surgery is performed almost exclusively under local anesthesia.[1] Older age or the presence of a chronic medical condition may be a contraindication for general anesthesia, except in particular situations such as an emergency involving multiple trauma or in pediatric or psychiatric patients. Peribulbar block is widely used in ophthalmic surgery to obtain ocular motor block as well as analgesia.

Complications include accidental puncture of intraocular structures, retrobulbar hematoma, and brainstem anesthesia.[2] Hyaluronidase is frequently used in addition to an anesthetic to improve peribulbar block and maintain baseline intraocular pressure.[3] However, anesthetic agents, used alone or in combination with hyaluronidase, are sometimes associated with toxic reactions.

Pharmacologic research has suggested that S(−)-enantiomers such as ropivacaine and levobupivacaine can reduce the cardiotoxicity and neurotoxicity of the original racemic mixtures, possibly because of enantio-selective effects.[4] The biologic effects of enantiomers differ, both quantitatively and qualitatively, due to receptor configuration. The R-isomer of bupivacaine produces a tonic block of sodium channels that is twice that produced by the L-isomer and a phasic block that is three times that of the L-isomer.[5] Levobupivacaine, an S(−)-enantiomer of a racemic mixture of bupivacaine, is a long-acting anesthetic[6,7] with less risk of cardiotoxicity and neurotoxicity compared with bupivacaine.[8–10] The recommended maximum single dose of levobupivacaine for peribulbar administration is 112.5 mg (15 mL in 0.5% solution), according to the information supplied by the manufacturer (Abbott Laboratories, Chicago, IL, USA). It is metabolized via the cytochrome P450 system and thus is contraindicated in patients with hepatic disease.[8]

The aim of this study was to compare the use of levobupivacaine and bupivacaine with and without addition of hyaluronidase for peribulbar block.

Materials and methods

A total of 160 patients scheduled for elective ophthalmic surgery were enrolled in this randomized, double-blind study which followed the tenets of the Declaration of Helsinki. Informed patient consent was obtained, and the study was approved by the institutional review board company, Umberto I Policlynic. The following exclusion criteria were used: previous allergic reaction to local anesthetics; mental illness; age younger than 18 years; retrobulbar hemorrhage; hepatic dysfunction; and anticoagulation therapy. The patients were standardized for gender, age, and general medical comorbidity, with the most frequent medical conditions being arterial hypertension, type 2 diabetes, and coronary heart disease. The demographic data for the patients are provided in Table 1 and the types of surgery are listed in Table 2.

The patients were premedicated with midazolam 1–3 mg intravenously and randomized into four groups of 40 each to receive one of four local anesthetic solutions for peribulbar anesthesia: levobupivacaine 0.5% (group L); bupivacaine 0.5% (group B); levobupivacaine 0.5% + hyaluronidase 10 IU/mL (group LH); or bupivacaine 0.5% + hyaluronidase 10 IU/mL (group BH). Peribulbar block was performed by two anesthetists and two ophthalmologists, in a ratio of 25% each. The total volume of anesthetic solution administered after aspiration to exclude intravascular needle placement varied in the range of 7–10 mL, according to orbit size and the increase in extraocular pressure. This volume was considered sufficient to obtain analgesia and motor block for the duration of surgery, while avoiding a dangerous increase in extraocular tone and the risks of oculocardiac reflex, ischemic neuropathy, and rarely amaurosis.[2,11] A single transpalpebral inferotemporal injection was performed perpendicularly to the skin and then directed at an angle of 45° for the entire length of the needle (25 G × 16 mm; BD® Microlance 3, Becton-Dickinson, BD Biosciences, Franklin Lakes, NJ, USA). After negative aspiration and in the absence of any sign of eyeball puncture or intramuscular penetration of the needle, the anesthetic mixture was administered over approximately 30 seconds.

Ocular compression was achieved by applying a pressure of 30 mmHg using a Honan balloon. This pressure was maintained for 15 minutes, while ocular akinesia was

Table 1 Characteristics of the four groups of patients

Characteristic	Group L n = 40	Group B n = 40	Group LH n = 40	Group BH n = 40	*P*
Men/women	17/23	16/24	19/21	18/22	0.917
Age (years)	72 ± 4.6	70 ± 8.4	72 ± 7.3	77 ± 8.7	0.007
Weight (kg)	66 ± 9.5	65 ± 11.2	64 ± 12.4	68 ± 9.6	0.372
Height (cm)	164 ± 10.7	161 ± 10.1	158 ± 10.2	161 ± 8.7	0.034
Volume of injection (mL)	8.4 (7–10)	8.50 (7.5–9.5)	9.2 (7–9)	9.0 (7–8.5)	0.239
Diabetes	8	6	9	7	0.844
Hypertension	18	21	21	23	0.735
Coronary disease	7	8	10	8	0.867

Note: The figures in brackets represent the minimum and maximum value of the parameter.
Abbreviations: L, levobupivacaine 0.5%; B, racemic bupivacaine 0.5%; LH, levobupivacaine + hyaluronidase 10 IU/mL; BH, racemic bupivacaine + hyaluronidase 10 IU/mL.

Table 2 Type of surgery and average intraocular pressure at baseline

Type of surgery	Mean IOP				*P**	*P***
	Group L n = 40	Group B n = 40	Group LH n = 40	Group BH n = 40		
Phacoemulsification	22 (16 ± 2)	23 (15 ± 2)	23 (13 ± 2)	27 (14 ± 2)	0.951	L vs LH < 0.001 L vs BH 0.001 B vs LH 0.001
Extracapsular extraction	5 (14 ± 3)	7 (16 ± 2)	4 (16 ± 3)	4 (16 ± 2)		>0.05
Glaucoma	7 (29 ± 5)	4 (28 ± 6)	5 (29 ± 2)	3 (30 ± 2)		>0.05
Secondary implantation	4 (13 ± 2)	3 (14 ± 2)	3 (15 ± 2)	–		>0.05
Cryotherapy	2 (38 ± 3)	3 (40 ± 2)	5 (36 ± 5)	6 (40 ± 3)		>0.05

Notes: *Calculated using the Chi-squared test with Yates correction; **analysis of variance, comparing group means. The figures in brackets represent the mean value ± the standard deviation of IOP.

Abbreviations: IOP, intraocular pressure; vs, versus; L, levobupivacaine 0.5%; B, racemic bupivacaine 0.5%; LH, levobupivacaine + hyaluronidase 10 IU/mL; BH, racemic bupivacaine + hyaluronidase 10 IU/mL.

examined every three minutes on five occasions. While the patients rotated their eyes in the vertical and horizontal directions, ocular akinesia was evaluated using a three-point system: (0) complete motor block for the direction examined; (1) 50% movement; and (2) full eye movement.[12] An akinesia score < 5 points was considered sufficient for surgery, although analgesia was also evaluated before surgery. Akinesia scores > 5 indicated a need for additional local anesthetic solution. Residual akinesia was evaluated 24 hours after surgery using the same scoring system, and persistent diplopia was evaluated by the ophthalmologist. Baseline intraocular pressure was measured in both eyes using an automated tonometer (Tonopen®, Mentor, Milan, Italy). The same blinded observer measured intraocular pressure after peribulbar block at the same intervals as for the akinesia evaluation.

Time to onset and duration of anesthesia were analyzed by analysis of variance, followed by the Student-Newman-Keuls test. The Chi-squared test was used to compare akinesia scores. An akinesia score between 0 and 3 was set as the target score corresponding to a successful block. Statistical significance was set at $P < 0.05$. The statistical analysis was done using the Statistical Package for the Social Sciences for Windows, release 19.0 (SPSS Inc, Chicago, IL, USA).

Results

Time to onset, duration of anesthesia, diplopia, and residual palpebral block at 24 hours are reported in Table 3. The time to onset for analgesia and akinesia did not differ significantly between levobupivacaine (12 ± 2.6 minutes) and racemic bupivacaine (13 ± 2.8 minutes). The combination of hyaluronidase and racemic bupivacaine noticeably shortened the time to onset and reduced intraocular pressure to normal or subnormal values. With durations of 185 ± 33.2 minutes and 188 ± 35.7 minutes in groups L and B, respectively, analgesia was significantly ($P < 0.001$) maintained beyond the surgical time and provided satisfactory pain control in the early postoperative period.

An akinesia score < 3 was found 15 minutes after peribulbar block (see Table 4). Complete akinesia (score 0) was obtained more frequently when hyaluronidase was used in addition to the anesthetic, with occurrences of 72.5% versus 57.5% in group LH versus L, respectively, and 67.5% versus 45% in group BH versus B. Incomplete akinesia occurred in fewer patients, but still in a fair number of cases.

Table 3 Study results

Parameter	Group L n = 40	Group B n = 40	Group LH n = 40	Group BH n = 40	*P*
Anesthesia onset (minutes)	12 ± 2.6	13 ± 2.8	11 ± 2.2	11 ± 2.1	B vs LH 0.0007 B vs BH 0.0006
Duration (minutes)	185 ± 33.2	188 ± 35.7	168 ± 22.5	176 ± 24.1	L vs LH 0.0089 B vs LH 0.0036
Diplopia	3 (7.5%)	4 (10%)	–	1 (2.5%)	0.153
Palpebral block	–	–	–	–	–
Ocular globe rotation	8 (20%)	11 (27.5%)	4 (10%)	4 (10%)	0.102

Abbreviations: L, levobupivacaine 0.5%; B, racemic bupivacaine 0.5%; LH, levobupivacaine + hyaluronidase 10 IU/mL; BH, racemic bupivacaine + hyaluronidase 10 IU/mL; vs, versus.

Table 4 Akinesia score

Score	Group L n = 40	Group B n = 40	Group LH n = 40	Group BH n = 40	*P*
0	23 (57.5%)	18 (45%)	29 (72.5%)	27 (67.5%)	0.571*
<3	12 (30%)	16 (40%)	8 (20%)	7 (17.5%)	
3–5	3 (7.5%)	4 (10%)	3 (7.5%)	6 (15%)	
>5	2 (5%)	2 (5%)	–	–	

Note: *P calculated with the Yates correction.
Abbreviations: L, levobupivacaine 0.5%; B, racemic bupivacaine 0.5%; LH, levobupivacaine + hyaluronidase 10 IU/mL; BH, racemic bupivacaine + hyaluronidase 10 IU/mL.

Table 5 Side effects

Side effects	Group L n = 40	Group B n = 40	Group LH n = 40	Group BH n = 40	*P*
Hypotension	4 (10%)	2 (5%)	1 (2.5%)	3 (7.5%)	0.545
Neurologic reaction	–	–	–	–	
Nausea	–	–	–	–	
Vomiting	–	–	–	–	
Shivering	–	–	–	1 (2.5%)	NA

Abbreviations: NA, not applicable; L, levobupivacaine 0.5%; B, racemic bupivacaine 0.5%; LH, levobupivacaine + hyaluronidase 10 IU/mL; BH, racemic bupivacaine + hyaluronidase 10 IU/mL.

The frequency of scores of 1–2 was 30% in group L, 40% in group B, 20% in group LH, and 17.5% in group BH. Scores of 3–5 occurred in 7.5% of group L, 4% of group B, 7.5% of group LH, and 6% of group BH. Two cases (5%) in group L and two cases in group B (5%) had a score > 5.

Analysis of variance showed a significant difference in time to onset of anesthesia between the groups, and especially between groups B and LH ($P < 0.001$) and between groups B and BH ($P < 0.001$). Time to onset did not differ significantly between groups L and LH. No significant difference was found comparing group L and group B. By analysis of variance, the duration of anesthesia was significantly different between groups B and LH ($P < 0.001$) and between groups L and LH ($P < 0.001$), but not between groups B and L, groups L and BH, or groups LH and BH.

The general akinesia score differed significantly between groups L and LH ($P = 0.043$, Chi-squared test) and groups B and LH ($P = 0.018$, Chi-squared test). The number of patients with a score of 0 was significantly different between groups B and LH ($P = 0.004$, Chi-squared test) and groups B and BH ($P = 0.017$, Chi-squared test).

External inferior rotation of the ocular globe, due to inhomogeneous diffusion of local anesthetic, occurred with a frequency of 20% in group L, 27.5% in group B, 10% in group LH, and 10% in group BH ($P = 0.102$).

Diplopia was not significantly different in the four groups ($P = 0.153$). It was observed in 2.5% of group BH, 7.5% of group L, and 10% of group B. No cases of residual palpebral ptosis occurred. Among the possible side effects, moderate hypotension (<30% of baseline) was observed in 10% of group L, 5.0% of group B, 2.5% of group LH, and 7.5% of group BH. One case (2.5%) of shivering was observed in group BH (see Table 5).

Discussion

Unlike our previous study, when only anesthetists were involved, in this study two anesthetists and two ophthalmologists, in a ratio of 50% each, performed the peribulbar anesthesia. The learning curve of the latter was rapid and satisfactory, as regards the percentages of success. We believe that this is related to correct identification of the injection point (inferotemporal region) outside of the conjunctival sheath, together with the use of a 25 G × 16 mm needle, which minimizes the risk of ocular lesions by reducing the depth of the injection. We did not need a longer needle to reach the ciliary ganglion; the local anesthetic was able to rotate around the eyeball, as confirmed by closing of the upper eyelid during the injection. Incorrect positioning of the needle tip may cause conjunctival chemosis and subconjunctival hemorrhage, which may result in increased intraocular pressure as a result of extraocular compression.

The onset of action of levobupivacaine (12 ± 2.6 minutes) and racemic bupivacaine (13 ± 2.8 minutes) is longer than many ophthalmic operations; this has obvious implications for the turnover of surgical patients. In the present study, addition of hyaluronidase to racemic bupivacaine significantly shortened the time to onset (13 ± 2.8 minutes versus 11 ± 2.1 minutes for racemic bupivacaine without versus with hyaluronidase, respectively). In contrast, hyaluronidase did not affect the time to onset of levobupivacaine-induced anesthesia (12 ± 2.6 minutes versus 11 ± 2.2 minutes with versus without hyaluronidase, respectively). These time intervals are shorter than previously reported onset times for levobupivacaine and for racemic bupivacaine with hyaluronidase (eg, 13 ± 5.6 minutes for levobupivacaine 0.75% + hyaluronidase 7.5 IU/mL and 11 ± 4.4 minutes for racemic bupivacaine 0.75% + hyaluronidase 7.5 IU/mL), despite a higher concentration of anesthetic.[11–13] Small differences in the block technique may explain the variability in results.

However, times to onset and motor blockade in our study were significantly longer and inadequate compared with those in another study.[13] Four minutes after anesthesia, without the addition of hyaluronidase, in three groups of patients that received 5 mL of a mixture of bupivacaine 0.5% and

lidocaine 2% (group 1), levobupivacaine 0.75% (group 2), and ropivacaine 1% (group 3), adequate operating conditions were achieved without any need for supplementary anesthesia.

A recent study reported similar results after administration of levobupivacaine 0.5% mixed with lidocaine 2% for superficial extraconal blockade.[14] The mixture of lidocaine and a long-term anesthetic (levobupivacaine or bupivacaine) had good results, without administration of hyaluronidase. Compared with topical anesthesia, peribulbar block is associated with greater risks,[8,15] although topical anesthesia may be more laborious for the surgeon in the case of patients who have difficulty in keeping the eye open and motionless.

Animal studies have shown a longer duration of action for levobupivacaine compared with racemic bupivacaine, probably reflecting the vasoconstrictive effect of levobupivacaine at lower doses, while time to onset may be related to its vasodilatory effect at higher doses.[16] Studies in humans have reported a similar potency for levobupivacaine compared with racemic bupivacaine,[17] but with less motor blockade and more minor cardiotoxicity using levobupivacaine than racemic bupivacaine.[18,19] According to our results, the time to onset of peribulbar block did not differ significantly between racemic bupivacaine and levobupivacaine (13 ± 2.8 minutes versus 12 ± 2.6 minutes, respectively).

Addition of hyaluronidase significantly shortened the time to onset for racemic bupivacaine and resulted in significant differences between groups L and BH, groups B and BH, and groups LH and BH. Addition of hyaluronidase did not significantly improve the time to onset for levobupivacaine, indicating that the vasoconstrictive effect of levobupivacaine is unfavorable for diffusion of local anesthetic, even in the presence of hyaluronidase.

The duration of peribulbar block was similar between racemic bupivacaine and levobupivacaine (188 ± 35.7 minutes versus 185 ± 33.2 minutes, respectively), groups L and BH (185 ± 33.2 minutes versus 176 ± 24.1 minutes), and groups LH and BH (168 ± 22.5 minutes versus 176 ± 24.1 minutes). However, there were significant differences in duration of peribulbar block between groups B and LH (188 ± 35.7 minutes versus 168 ± 22.5 minutes), groups B and BH (188 ± 35.7 minutes versus 176 ± 24.1 minutes), and groups L and LH (185 ± 33.2 minutes versus 168 ± 22.5 minutes), because of the effect of hyaluronidase on anesthetic block.

Controversy remains regarding the combination of local anesthetics and hyaluronidase with respect to efficacy, duration, and side effects.[20–22] Hyaluronidase causes an increase in pH that is directly proportional to the amount administered[23] and enhances diffusion of anesthetic into the nerves without increasing the plasma drug concentration.[24]

Our results demonstrate a shortening of time to onset and duration of analgesia together with improved akinesia. Patients frequently reported partial or complete areas of analgesia in the frontal and maxillary regions with anesthesia of the superior homolateral dental arch. Some authors[25] have suggested a negative interaction between hyaluronidase and epinephrine with regard to time to onset of anesthesia, but an additive effect with respect to the peak area of the anesthesia. Hyaluronidase may have a similar interaction with levobupivacaine, which has a vasoconstrictor effect.[25]

The motor block after levobupivacaine was better than after racemic bupivacaine, and hyaluronidase positively influenced the number of patients with an akinesia score of 0. This improvement in akinesia[21] may be explained by the lower percentage of inferotemporal globe rotation in the presence of hyaluronidase (20%–27.5% versus 10%–10% rotation without versus with hyaluronidase, respectively). A previous study[11] reported residual next-day akinesia in 60% of patients after levobupivacaine and in 72% of patients after racemic bupivacaine, as well as persistent diplopia in 40% and 52% of patients, respectively. In our study, no cases of residual akinesia were recorded at 24 hours, and diplopia was found only in groups L (7.5%) and B (10%). These different results may be explained by the difference in concentration of the local anesthetic (0.75% versus 0.50%) or in the dose of hyaluronidase (7.5 IU/mL versus 10 IU/mL).[15,27]

Among the possible side effects, hypotension (–30% of baseline) was seen in a limited number of cases (10% of group L, 5% of group B, 2.5% of group LH, and 7.5% of group BH). No medical treatment was necessary.

Overall, our results confirm those of a previous study,[28] and demonstrate that: these local anesthetics are effective in assuring analgesia and akinesia compatible with ophthalmic surgery; duration of anesthetic block is similar between levobupivacaine and racemic bupivacaine; when akinesia is incomplete, the surgery may be difficult; time to onset does not differ significantly between levobupivacaine and racemic bupivacaine; and the combination of an anesthetic agent and hyaluronidase shows improved efficacy with regard to motor block and time to onset. The results do not suggest superior efficacy of levobupivacaine compared with racemic bupivacaine, because of their similar activity as regards time to onset, duration of action, and motor block. Based on our experience of ophthalmic surgery in elderly patients, levobupivacaine is a suitable anesthetic because of its limited

neurotoxicity and low cardiotoxicity, which represents a valid reason for use of levobupivacaine.

Disclosure

The authors report no conflicts of interest in this work.

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