**Abstract. – Aims:** The Authors examine the employment of a new anaesthetic agent, levobupivacaine 0.50% (S-enantiomer of racemic mixture of bupivacaine), for peribulbar anaesthesia in a randomized double blind study vs. racemic bupivacaine 0.50% alone or in association with hyaluronidase 10 IU.ml⁻¹.

**Materials and Methods:** 120 patients were divided into four groups of 30 each: group L (levobupivacaine 0.50%), group B (racemic bupivacaine 0.50%), group LH (levobupivacaine – hyaluronidase 10 IU.ml⁻¹), group BH (racemic bupivacaine – hyaluronidase 10 IU.ml⁻¹).

**Results:** The onset-time (14±3.2 min vs. 13±4.8 min) and the duration of anaesthesia (195±34.2 vs. 204±37.6) were similar. The ocular akinesia was evaluated with an 8 pointsystem: it was considered sufficient for surgery with values of less than 5 points. The association with hyaluronidase increased the spread of local anaesthetics (76.6% of group LH, 73.3% of group BH) with local anaesthetics alone (60% of group L, 56.6% of group B).

Moderate hypotension (<30% baseline) was reported in 3 patients (10%) of group L, 2 (6.6%) of group B, 1 (3.3%) of group LH and 2 (6.6%) of group BH. Statistical analysis (Student-Newman-Keuls test) was significant between group L vs. BH, B vs. BH and LH vs. BH as regards onset-time of anaesthesia; between group B vs. LH, B vs. BH and L vs. LH for the duration of anaesthesia.

**Conclusions:** In conclusion levobupivacaine, a longlasting local anaesthetic with limited cardio and neurotoxicity, might be useful for vitreoretinal surgery in elderly patients, compared with general anaesthesia.

**Key Words:** Anaesthetics, Levobupivacaine, Racemic bupivacaine, Ophthalmic surgery, Peribulbar block.

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**Introduction**

At present, ophthalmic surgery is almost exclusively performed in local anaesthesia¹. Elderly patients and the presence of chronic medical diseases exclude, except particular situations (emergencies in polytraumatism, paediatric and psychiatric patients), recurrence to general anaesthesia.

Peribulbar block is widely employed in ophthalmic surgery to obtain ocular motor block besides analgesia. Complications include accidental puncture of intraocular structures, retrobulbar hematoma and brainstem anaesthesia².

Hyaluronidase is frequently added to the anaesthetic solution to improve peribulbar block and to maintain baseline intraocular pressure (IOP)³. The anaesthetic agents are used alone or in association to obtain analgesia and motor block with poor toxic reactions. The pharmacological research suggests new anaesthetics, S (-) enantiomers of racemic mixtures, such as ropivacaine and levobupivacaine, to reduce cardiotoxicity, probably enantiomeric⁴ and neurotoxicity.

The biological effects of enantiomers are different, both quantitatively and qualitatively, due to the receptor’s configuration.

The R-isomer of bupivacaine produces a tonic block of sodium channels two times longer and a phasic block three times greater than L-isomer⁵. Levobupivacaine is a S (-) enantiomer of racemic mixture of bupivacaine; it is a long acting anaesthetic with a lower risk of cardiotoxicity and neurotoxicity with bupivacaine⁶-¹⁰. The recommended maximum single dose for peribulbar administration, according to Abbott laboratories summary of characteristics is 112.5 mg (15 ml – 0.50%), while its metabolism through the
Table I. Demographic data of the case load.

<table>
<thead>
<tr>
<th></th>
<th>L (n 30)</th>
<th>B (n 30)</th>
<th>L H (n 30)</th>
<th>B H (n 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>14/16</td>
<td>12/18</td>
<td>17/13</td>
<td>11/19</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>71 ± 6.4</td>
<td>71 ± 8.9</td>
<td>73 ± 7.6</td>
<td>75 ± 9.1</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>64 ± 9.8</td>
<td>66 ± 10.2</td>
<td>62 ± 10.4</td>
<td>64 ± 11.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 ± 11.4</td>
<td>165 ± 12.1</td>
<td>163 ± 10.9</td>
<td>163 ± 9.8</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>8.4 (7.0-10)</td>
<td>8.80 (7.5-9.5)</td>
<td>9.4 (7.0-9.0)</td>
<td>9.0 (7.0-8.5)</td>
</tr>
</tbody>
</table>
Once daily Latanoprost-Timolol in POAG

Table II. Types of surgical operations.

<table>
<thead>
<tr>
<th></th>
<th>L (n 30)</th>
<th>B (n 30)</th>
<th>L H (n 30)</th>
<th>B H (n 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phacoemulsification</td>
<td>21</td>
<td>22</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Extracapsular extraction</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Secondary implantation</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Criotherapy</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Statistical analysis for onset time and duration of anaesthesia was performed using analysis of variance followed by the Student-Newman-Keuls test, while Chi square test was applied for comparison of akinesia scores. Results are means ± SD. A p value of less than 0.05 was considered significant. We considered an akinesia score between 0 and 3 as the target corresponding to a successful block.

Results

Onset-time, duration of anaesthesia, diplopia and residual palpebral block at 24 hours are reported in Table III.

Onset-time for analgesia and akinesia was almost the same for levobupivacaine and racemic bupivacaine (14±3.2 vs. 13±4.8 min).

The association of hyaluronidase and local anaesthetics sensibly shortened onset-time and reduced intraocular pressure to normal or subnormal values. The duration of analgesia outlasted surgical time and provided satisfactory pain control in the early postoperative period (145 min L vs. 240 min B).

Incidence of diplopia was observed in 6.6% of group L and 10% of group B; residual palpebral ptosis was found in no case.

Akinesthesia score (96% confidence interval) of less than 3 was examined 15' after peribulbar block (Table IV). Complete akinesia (score 0) was obtained more frequently with the association of hyaluronidase (76.6% of group LH, 73.3% of group BH) respective to local anaesthetic alone (60% of group L, 56.6% of group B). Incomplete akinesia took place in a lower but significant number of patients:

- 0< score <3 30% of group L, 40% of group B, 20% of group LH, 23.3% of group BH;
- 3< score <5 6.6% of group L, 3.3% of group B, 3.3% of group LH, 3.3% of group BH;
- score >5 no case.

The external inferior rotation of the ocular globe due to inhomogeneous diffusion of local anaesthetic was of 20.6% in group L, 33.3% in group B, 13.3% in group LH and 10% in group BH.

Among side effects (see Table V) we observed moderate hypotension (<30% baseline) in 10% of group L, 6.6% of group B, 3.3% of group LH and 6.6% of group BH. One case (3.3%) of shivering was observed in group BH.

Statistical analysis emphasized significant differences with analysis of variance as regards onset-time of anaesthesia; Student-Newman-Keuls test reported positivity between group L vs. BH.

Table III. Results. Onset-time and duration for analgesia and akinesia, diplopia and residual palpebral block at 24 hours. Occurrence of ocular globe rotation.

<table>
<thead>
<tr>
<th></th>
<th>L (n 30)</th>
<th>B (n 30)</th>
<th>L I (n 30)</th>
<th>B I (n 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthesia onset (min)</td>
<td>14 ± 3.2</td>
<td>13 ± 4.8</td>
<td>12 ± 3.1</td>
<td>10 ± 2.6</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>195 ± 34.2</td>
<td>204 ± 37.6</td>
<td>171 ± 24.8</td>
<td>184 ± 28.1</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2 (6.6%)</td>
<td>4 (13.3%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Palpebral block</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ocular globe rotation</td>
<td>8 (20.6%)</td>
<td>10 (33.3%)</td>
<td>4 (13.3%)</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>
of B vs. BH and LH vs. BH, non significant between group L vs. LH. No test is possible between group L vs. B and group B vs. LH.

The duration of anaesthesia evidenced positive test with analysis of variance; Student-Newman-Keuls test reported significant differences between group B vs. LH, B vs. BH, L vs. LH, non significant between B vs. L, L vs. BH, LH vs. BH.

Chi square test for the general akinesia score showed positive result in group L vs. LH \( (p=0.043) \) and B vs. LH \( (p=0.018) \). As regards the score 0, test reported significant values between group B vs. LH \( (p=0.004) \) and B vs. BH \( (p=0.017) \) (Figure 1).

**Discussion**

Onset-time of levobupivacaine \( (14\pm3.2 \text{ min}) \) and racemic bupivacaine \( (12\pm3.1 \text{ min}) \) is not much longer than the duration of many operations itself, slowing down the patient’s rotation.

Statistical analysis reported a significant shortening of onset-time of racemic bupivacaine with hyaluronidase with the same anaesthetic alone \( (10\pm2.6 \text{ vs. } 13\pm4.8 \text{ min}) \).

On the contrary levobupivacaine with hyaluronidase showed no significant differences with respect to levobupivacaine alone \( (12\pm3.1 \text{ vs. } 14\pm3.2 \text{ min}) \). These values are better than those of other Authors\(^1\) \( (13\pm5.6 \text{ min with levobupiva-} \text{caine } 0.75\% + \text{ hyaluronidase } 7.5 \text{ IU/ml and } 11\pm4.4 \text{ min with racemic bupivacaine } 0.75\% + \text{ hyaluronidase } 7.5 \text{ IU/ml}) \). Although higher local anaesthetic concentration was employed, onset-time resulted longer.

Most probably small differences of block technique may explain the variability of results.

Peribulbar block is much more dangerous\(^8,13\) than topical anaesthesia. However, the latter may favour accidental ocular lesions, incomplete conjunctival analgesia, corneal damage and difficulty in modifying the intraoperative surgical technique.

Animal studies showed a higher potency of levobupivacaine vs. racemic bupivacaine probably due to a vasoconstrictor effect of levobupivacaine at lower doses and a vasodilatative effect at higher doses\(^{14}\).

Human studies reported similar potency of racemic bupivacaine and levobupivacaine\(^{15}\), with a lower motor block and minor cardiotoxicity of levobupivacaine\(^{16,17}\).

According to our data onset-time of peribulbar block of racemic bupivacaine and levobupivacaine alone are statistically not comparable \( (13\pm4.8 \text{ vs. } 14\pm3.2 \text{ min}) \).

Significant differences exist between local anaesthetics alone and in association with hyaluronidase (group L vs. BH, group B vs. BH and group LH vs. BH) with a prevalence of lower onset-time for racemic bupivacaine.

Even the comparison between group L vs. LH is not significant, making evident that the association of levobupivacaine with hyaluronidase does not improve onset-time.

**Table IV.** Akinesia score.

<table>
<thead>
<tr>
<th>Score</th>
<th>L (n 30)</th>
<th>B (n 30)</th>
<th>LH (n 30)</th>
<th>BH (n 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60% (18)</td>
<td>56.6% (17)</td>
<td>76.6% (23)</td>
<td>73.3% (22)</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>30% (9)</td>
<td>40% (12)</td>
<td>20% (6)</td>
<td>23.3% (7)</td>
</tr>
<tr>
<td>3-5</td>
<td>6.6% (2)</td>
<td>3.3% (1)</td>
<td>3.3% (1)</td>
<td>3.3% (1)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>3.3% (1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table V.** Side effects.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>L (n 30)</th>
<th>B (n 30)</th>
<th>LH (n 30)</th>
<th>BH (n 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>10% (3)</td>
<td>6.6% (2)</td>
<td>3.3% (1)</td>
<td>6.6% (2)</td>
</tr>
<tr>
<td>Neurologic reactions</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nausea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Shivering</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.3% (1)</td>
</tr>
</tbody>
</table>
The vasoconstrictor effect of levobupivacaine is unfavorable for the diffusion of local anaesthetic, even in the presence of hyaluronidase.

Peribulbar block evidenced a similar duration of racemic bupivacaine and levobupivacaine alone (204 ± 37.6 vs. 195 ± 34.2 min), of group L vs. BH and of group LH vs. BH. Significant differences are between group B vs. LH, group B vs. BH and group L vs. LH as though hyaluronidase shortens the duration of anaesthetic blockade.

There is still controversy about the association of local anaesthetics and hyaluronidase as regards efficacy, duration and side effects\(^{18-20}\).

Hyaluronidase causes an increase of pH, directly proportional to the administered amount\(^{21}\), of its nerve diffusion without a rise in plasmatic concentration\(^{22}\).

Our results emphasized a shortening of onset-time and of the duration of analgesia with improvement of akinesia at the preoperative control. Frequently, patients reported partial or complete areas of analgesia in the frontal and maxillary region with anaesthesia of the superior omolateral dental arch.

Some Authors\(^{23}\) suggest a negative interaction (inhibition) between hyaluronidase and ephinephrine as regards onset-time of anaesthesia but an additional effect as regards the size of the peak area of anaesthesia. Hyaluronidase could produce a similar interaction with levobupivacaine, which has vasoconstrictor effect\(^{24}\).

As regards motor block, this was lower after levobupivacaine than racemic bupivacaine, while hyaluronidase influence positively score 0; its improvement on akinesia\(^{19}\) could explain the lower percentage of inferotemporal globe rotation (20.6-33.3 vs. 13.3-10% respectively).

Previous experiences\(^{11}\) reported residual akinesia on the following morning, even in 60% of patients post levobupivacaine and in 72% patient post racemic bupivacaine; persistent diplopia in 40% and 52% of patients respectively.

In our study no case of residual akinesia at 24h was recorded; diplopia resulted in group L (6.6%) and in group B (10%).

Partially differences can be explained by the different concentration of local anaesthetics (0.75 vs. 0.50%) and by the lower dosage of hyaluronidase (7.5 IU/ml\(^{-1}\) vs. 10 IU/ml\(^{-1}\)).

Among side effects hypotension (–30% baseline) resulted in a limited number of cases (10% of group L, 6.6% of group B, 3.3% of group LH, 6.6% of group BH); no medical treatment was necessary.

On the whole, examination of our findings allows the following considerations:

- the local anaesthetics employed are fit for assuring analgesia and akinesia compatible with ophthalmosurgery operations;
- the duration of anaesthetic block of levobupivacaine and racemic bupivacaine is similar; akinesia may result incomplete and insufficient;
- onset-time of levobupivacaine;
- association of anaesthetic agents with hyaluronidase improves the final result.

The long lasting effect of levobupivacaine, alone or in association with hyaluronidase is justified in vitreoretinal surgery, though lower motor block may be a restriction.
At present, limited incidence of central nervous system toxicity and cardiotoxicity represents the only reason to prefer levobupivacaine to racemic bupivacaine, particularly in elderly patients.

References

11. MCLURE HA, RUBIN AP. Comparison of 0.75% levobupivacaine with racemic bupivacaine for peribulbar anaesthesia. Anaesthesia 1988; 53: 1160-1164.