Efficacy of varying concentrations of hyaluronidase in peribulbar anaesthesia

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We have compared the efficacy of adding varying concentrations of hyaluronidase to a standard mixture of 2% lidocaine and 1% ropivacaine to provide peribulbar anaesthesia for cataract surgery. We used (i) the time to adequate anaesthesia for surgery and (ii) ocular and eyelid movement scores at 8 min after block as clinical endpoints. Ninety patients were randomly allocated to receive 7–10 ml of equal volumes of 2% lidocaine and 1% ropivacaine without hyaluronidase or with hyaluronidase 15 IU ml⁻¹ or 150 IU ml⁻¹. Median time at which the block was adequate for surgery was 6 min in all groups (interquartile range 4–12 min). Median eyelid movement scores were similar in all groups, but the ocular movement scores at 8 min were significantly lower in the group which received hyaluronidase 150 IU ml⁻¹ than in the group not given hyaluronidase (P<0.03). There were no differences between groups in the incidence of minor complications. A high concentration of hyaluronidase resulted in a statistically significantly lower ocular movement score at 8 min; the clinical relevance of this finding is uncertain.

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Regional anaesthesia is the technique of choice for the vast majority of patients undergoing cataract surgery. Peribulbar anaesthesia is considered safer than injections inside the extraocular muscle cone, especially when non-ophthalmologists perform the block. A mixture of bupivacaine and lidocaine is the most frequently used local anaesthetic combination, with hyaluronidase and epinephrine frequently added in various concentrations to this mixture. Hyaluronidase hydrolyses the C1–C4 bonds between glucosamine and glucuronic acid in ground substance,
thus promoting spread of the anaesthetic through the tissue. The proposed advantages of using hyaluronidase include enhanced speed of onset and improved operating conditions. There are, however, conflicting data about the advantages of hyaluronidase in peribulbar anaesthesia. Concentrations as low as 7.5 IU ml\(^{-1}\) have been reported to be effective,\(^1\) whereas other studies found no benefit at a higher concentration of 150 IU ml\(^{-1}\).\(^2\) We found in a previous study\(^3\) that excellent operating conditions were achieved in a median time of 8 min using the low concentration of 15 IU ml\(^{-1}\), as recommended by the British National Formulary,\(^4\) added to equal volumes of 2% lidocaine and 0.75% bupivacaine and to 1% ropivacaine. Concerns have been expressed about the use of hyaluronidase as it involves injecting a foreign protein into the orbit with the risk of sensitization and allergic reactions if re-injected. As many patients need cataract surgery twice, it is pertinent to ascertain if the addition of hyaluronidase to the anaesthetic mixture is necessary. We compared, therefore, the efficacy of anaesthesia obtained with the standard concentration of 15 IU ml\(^{-1}\) hyaluronidase, no hyaluronidase and a high concentration of 150 IU ml\(^{-1}\).

### Methods and results

Following hospital Ethics Committee approval and written informed consent, we studied 90 patients presenting for cataract surgery under local anaesthesia. Patients were excluded if they were unwilling to take part, if there were communication or language problems, or if there was a history of allergy to amide-type local anaesthetic agents. Patients were randomly allocated to one of three groups using a random number table. All patients received an equal volume of 1% ropivacaine and 2% lidocaine. In group 1 no hyaluronidase was added to the anaesthetic mixture and in groups 2 and 3 hyaluronidase was added to give a final concentration of 15 and 150 IU ml\(^{-1}\), respectively. The anaesthetic solution was warmed to body temperature.

Patients were not fasted and did not receive any premedication, perioperative sedation or supplemental oxygen. On arrival in the induction room, baseline eyelid and globe movements were assessed. Topical anaesthesia of the conjunctiva and cornea was achieved by administring two or three drops of 0.4% oxybuprocaine. Standard monitoring was commenced and i.v. access established. Peribulbar block was carried out, by one of two consultant anaesthetists, via a single transcutaneous inferolateral injection using a 25-gauge, 25 mm needle directed backwards in a sagittal plane, tangentially to the globe and parallel to the floor of the orbit. The bevel of the needle faced the globe. Following test aspiration, 8 ml of the local anaesthetic mixture was injected over 30–40 s (range 7–10 ml to allow for very heavy or very frail patients). Different volumes of local anaesthetic were used depending on the degree of filling of the orbit observed during the injection and the rate of onset of ptosis during injection. An additional facial nerve block was not required, as akinesia of the orbicularis oculi was achieved by a peribulbar block. Manual compression and gentle massage of the eyeball were performed, after which a Visitec intraocular pressure reducer, inflated to 40 mm Hg, was applied between scoring. Eyelid and ocular movements were assessed at 2 min intervals with a scoring system described previously.\(^3\) Scoring was carried out by an independent, trained observer, who was blinded as to which anaesthetic mixture the patient had received.

Ocular movements were scored for each direction of gaze in a superior, inferior, medial and lateral direction with a maximum score for each direction of three points and therefore a possible maximum total of 12 points. Ocular and eyelid movements were assessed at 2, 4, 6 and 8 and 10 min until the block was considered adequate for surgery. If the block was inadequate after 10 min, supplementary anaesthesia was provided with a further injection of up to 5 ml of the test solution, by the same technique. The time to adequate surgical anaesthesia was noted as well as the need for supplementary anaesthesia. It was assumed that, once motor block had been achieved, adequate sensory block was already present, as this precedes motor block. Complications during or after injection were recorded and patients were specifically questioned about pain during insertion of the block, or during surgery.

Outcome criteria were defined as the time needed to reach adequate block to start the operation and the difference in median ocular and eyelid movement scores at 8 min; differences between groups were analysed by Kruskal–Wallis one-way analysis of variance (ANOVA) for non-parametric data. Post hoc analysis was undertaken with the Mann–Whitney test; a P-value of ≤0.03 was considered statistically significant. The number of patients who reached an ocular movement score of 0 or 1, the need for further injections, delays to the start of surgery and the occurrence of complications were compared using \(\chi^2\) or Fischer’s exact test, as appropriate. Statistical analysis was carried out using SPSS 8.0 package for Windows 95.

| Table 1 | Median (interquartile range) ocular and eyelid movement scores and time to anaesthesia. *P<0.03 for difference between no hyaluronidase and hyaluronidase 150 IU ml\(^{-1}\) |
|----------------|---------------------------------|-----------------|-----------------|
|                | Ocular movement                 | Hyaluronidase   |                 |
|                | No hyaluronidase                | 15 IU ml\(^{-1}\) | 150 IU ml\(^{-1}\) |
| 2 min          | 1 (0–1)                         | 1 (0–1)         | 1 (0–1)         |
| 4 min          | 2 (0–6)                         | 0 (0–4)         | 0 (0–1)*        |
| 6 min          | 3 (0–5)                         | 2 (0–6)         | 0 (0–2)         |
| 8 min          | 4 (0–4)                         | 0 (0–4)         | 0 (0–1)         |

P-value of \(\chi^2\) or Fischer’s exact test, as appropriate.
The three groups were similar in age, sex and mean axial length of the globe. There were 30 patients in group 1, 31 in group 2 and 29 in group 3 because one patient was mistakenly assigned to the wrong group. The mean (range) ages were 73 (46–91) yr in group 1, 71 (54–88) yr in group 2 and 74 (51–91) yr in group 3. The male:female ratio was 10:20 in group 1, 15:16 in group 2 and 12:17 in group 3. The mean (SD) axial length was 23.6 (1.4) mm in group 1, 24.1 (1.7) mm in group 2 and 23.4 (1.3) mm in group 3.

The median time at which patients were adequately anaesthetized was 7 min in group 1, 6 min in group 2 and 4 min in group 3 (P=0.089). Median ocular movement scores at 8 min were significantly lower in group 3 than in group 1 (P=0.014) which was the other predefined endpoint (Table 1). Twenty-three patients in group 3 achieved ocular movement scores of ≤1, compared with 16 in group 1 and 18 in group 2 (P=0.088). There was no significant difference between groups in terms of requirements for supplementary anaesthesia: 10 patients in group 1, nine in group 2 and four in group 3 required additional anaesthesia. Four patients in group 1, two in group 2 and one in group 3 sustained minor complications.

Comment

We have shown that hyaluronidase at a concentration of 150 IU ml⁻¹ resulted in a significantly lower ocular movement score at 8 min and this was associated with a non-significant improvement in speed of onset of the block.

Hyaluronidase is of ovine origin and acts by hydrolysing the C1–C4 bonds between glucosamine and glucuronic acid. It depolymerizes the glycosaminoglycan-rich ground substance which normally obstructs intercellular diffusion. It has been suggested that hyaluronidase increases the permeability of the fibrous septa which compartmentalize the orbital contents, thereby enhancing the uniform spread of local anaesthetic.⁵

Studies have produced widely conflicting results on the possible advantages of using hyaluronidase, but these differences may arise partly from a number of confounding variables, including the choice of anaesthetic solution, injection site and techniques, as well as the pH of the anaesthetic solution. Morsman and Holden found improved anaesthetic conditions with hyaluronidase at a concentration of 50 IU ml⁻¹.⁵ Sarvela and Nikki observed similar improvements with a concentration of 7.5 IU ml⁻¹; no additional benefit was found when the concentration was doubled.¹ Two studies found that hyaluronidase at a concentration of 10–15 IU ml⁻¹ improved the efficacy of peribulbar block when the anaesthetic solution was alkalinized to a pH of 6.7.⁶ ⁷ Conversely, Lewis and colleagues observed a faster onset with pH-adjusted anaesthetic solution, but no difference in time to complete anaesthesia between patient groups, all of whom received hyaluronidase 15 IU ml⁻¹, and indeed increased requirements for supplementary anaesthesia in the pH-adjusted group.⁸ In contrast, other more recent studies have observed no benefit when using hyaluronidase at concentrations of 25, 50 or 150 IU ml⁻¹,² ⁹ ¹⁰ and improved speed of onset of block only when used in a concentration of 300 IU ml⁻¹.¹¹

Our standard practice is to inject 8 ml of local anaesthetic mixture; rarely, very small or very large patients received a slightly smaller or greater volume. Nevertheless, it is unlikely that the differences in speed of onset of block found in this study are the result of differences in dose of local anaesthetic. In our study, an experienced consultant anaesthetist performed all blocks, and this probably resulted in the short time to adequate anaesthesia. In this situation, the use of hyaluronidase confers no practical advantages and we cannot recommend it. However, when anaesthetic trainees are learning peribulbar anaesthetic techniques, hyaluronidase may be useful in compensating for a less expert technique.

References

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