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Original Article

# Does the addition of hyaluronidase improve the quality of peribulbar anesthesia in cataract surgery? – A randomized double blinded study

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## Abstract

*Purpose:* To determine the necessity of hyaluronidase as an anesthetic adjuvant for peribulbar anesthesia during cataract surgery and to assess differences in anesthetic outcomes in the absence of hyaluronidase.
*Methods:* In this double blinded randomized study, 202 patients reporting for surgery for senile cataract in their first eye under regional ocular anesthesia without pre-existing extra ocular movement restriction were randomly divided into 2 groups: Group 1 – anesthesia without hyaluronidase, Group 2 – anesthesia with 50 IU/ml Hyaluronidase. Peribulbar block with 5 ml of anesthetic mixture of 2% lignocaine with 1:200000 adrenaline and 0.5% bupivacaine with or without hyaluronidase was performed with 3 ml deposited in the infero-medial quadrant and 2 ml in the supero-medial quadrant followed by ocular massage. Surgeons' score for akinesia, patients' score for analgesia, augmentation of block if any and extra ocular movements on first post-operative day were compared between the groups.
*Results:* There was no statistically significant difference between the two groups in akinesia ($p = 0.22$, 0.68 and 0.98), analgesia ($p = 0.44$ and 0.09) or requirement of anesthetic augmentation ($p = 0.3$). Extraocular movement restriction was not noted in any patient. Onset of akinesia and analgesia was earlier in Group 2 ($p = 0.004$ and $p = 0.005$ respectively).
*Conclusions:* Hyaluronidase is not an essential adjuvant for peribulbar block for cataract surgeries. Appropriate deposition of a smaller volume of anesthetic agent and adequate ocular massage provide adequate and safe anesthesia.

**Keywords**: Peribulbar anaesthesia, Hyaluronidase, Manual small incision cataract surgery, Ocular anaesthesia, Ocular analgesia


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## Introduction

A sine qua non for any surgery is the absence of pain for the entire duration of the surgical procedure. Performing ophthalmic surgery under local anesthesia needs the provision of anesthesia and akinesia to ensure a cooperative patient and ideal conditions for the surgeon. Peribulbar anesthesia remains the popular choice for cataract surgeries and has a proven record of achieving both anesthesia and akinesia.[1]

The complex system of connective tissue membranes dividing the orbital space has the potential to impede the spread of local anesthesia to reach the relevant motor and sensory nerves.[2] This has resulted in the use of adjuvants such as hyaluronidase, epinephrine, bicarbonates, muscle relax-

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ants, opiates and clonidine to enhance the ophthalmic regional anesthesia.[3]

Of these, hyaluronidase has been the most common additive to ocular anesthesia and is believed to increase tissue permeability and spread of anesthesia by its depolymerising and hydrolysing action on the glycosaminoglycan, hyaluronan.[4]

Nevertheless, this purported role of hyaluronidase has been called into question and a consensus on its suitability in regional ocular anesthesia is still elusive.[5]

The purpose of this study was to determine the necessity of hyaluronidase as an anesthetic adjuvant for peribulbar anesthesia during cataract surgery and to assess differences in anesthetic outcomes, if any, in the absence of hyaluronidase.

## Materials & methods

In this randomized double blinded study, participants were recruited over a 15-month period (February 2015–May 2016) after approval had been obtained from the Institute Ethics and Research Committee (ECR/451/Inst/PY/2013). Adult patients who reported for surgery for senile cataract (first eye only) under regional ocular anesthesia were included. Those patients with pre-existing extra ocular movement restriction and requiring sedation/general anaesthesia or with systemic contraindication to the use of adrenaline in 1:200000 concentration as noted by the physician during pre operative work up were excluded. Also, one eyed patients, inflamed eye like phacolytic, phacomorphic glaucomas, those with pupillary dilatation of <6 mm who would require iris manipulation to deliver the nucleus were not included in the study. Informed written consent was obtained from all participants. The cataract extraction (Manual Small Incision Cataract Surgery) was performed in all patients by a qualified specialist/consultant ophthalmologist.

202 patients were randomly divided into two groups – Group 1: Without Hyaluronidase and Group 2: With Hyaluronidase (50 IU/ml). Randomisation was done by computer generated random numbers on a day to day basis depending on the number of cases allotted to consultants that day. All patients received peribulbar block with anesthetic mixture of 3 ml of 2% lignocaine and adrenaline (1:200000) and 2 ml of 0.5% bupivacaine with or without hyaluronidase. This was administered by a single ophthalmologist (SN) who was blinded to the solution used. With the gaze fixed ahead in the primary position, 3 ml of the anesthetic solution was deposited inferomedially. Ocular massage was given for 30 s by hand followed by another injection of 2 ml superomedially.[6] The stop clock was started on withdrawal of the needle after the first inferomedial injection. Ocular massage was repeated for another 60 s to promote the spread of the local anesthetic and softening of the globe. Extra ocular movements were assessed. In case of absence of restriction of extra ocular movements, further ocular massage was given for another 2 min and reassessed. If the patient could still perform full extraocular movement, a repeat peribulbar block of 2 ml of the same anesthesia was given in the inferomedial quadrant. Absence of corneal sensation was considered as satisfactory analgesia and time taken for onset of akinesia and analgesia was recorded.

**Table 1**. Surgeon score card.

| |
|---|
| **Extra ocular movements** |
| Fully blocked throughout the procedure |
| Minimal movements |
| Moderate movements |
| Full movements |
| Blocked but movements recovered before end of surgery |
| **Ease of procedure** |
| No difficulty |
| Slight difficulty |
| Moderate difficulty |
| Analgesia supplementation required (if so, what?) |
| **Orbicularis oculi action** |
| Fully blocked throughout the procedure |
| Minimal squeezing of lids |
| Moderate squeezing of lids |
| Marked squeezing of lids and supplement facial block required |
| Squeezing of lids recovered before end of surgery |

All patients were shifted to the Ophthalmic Operation theatre within 10 min of the recorded observation of restriction in extraocular movements. A reliable confirmation of adequacy of analgesia could be done by the patient's reaction to the insertion of the superior rectus bridle suture at the start of surgery. If either the surgeon or patient deemed akinesia/analgesia obtained to be inadequate, the block was supplemented with a subconjunctival injection. (2% lignocaine with 1:200000 adrenaline; 0.3–0.5 ml).

The operating surgeon was asked to document any difficulty due to the anesthesia during the procedure (Table 1). Post operatively the patient was given a visual analogue scale (0–10) to grade the perceived pain at the beginning of surgery and end of surgery Extra ocular movements were assessed on the 1st post-operative day to observe for any restriction in extraocular movements.

The results were analysed using the Statistical Package for Social Sciences (SPSS, version 23) and a p value of <0.05 was considered significant. Comparison of the two groups was to be by independent t tests or Mann-Whitney U test depending on the distribution of the data. Akinesia and analgesia were also represented by Box-Whisker plots.

## Results

There were 100 patients in group 1 and 102 patients in group 2. The characteristics of the two patient groups are shown in Table 2 and there were no significant differences in respect to age, sex and diabetes mellitus. Shapiro-Wilk test revealed skewed deviation of the data (Sig $\leq$ 0.05) and Mann-Whitney U test was used to compare the two groups.

In group 1, the time for onset of akinesia ranged between 1.5 and 5.5 min (mean 2.5 ± SD 0.7; 95% CI: 2.4–2.6 min) and for onset of analgesia was between 1.5 and 4.25 min (mean 2.3 ± SD 0.5; 95% CI: 2.2–2.4 min). In group 2 the onset of akinesia and analgesia was 1.5–5 min (mean 2.3 ± SD 0.6; 95% CI: 2.2–2.4 min) and 1.4–3.5 min (mean 2.2 ± SD 0.4; 95% CI: 2.1–2.2 min) respectively. The difference in time for onset of akinesia and analgesia was statistically significant between the two groups (p = 0.004 and p = 0.005 respectively), but, a closer examination shows the mean difference between the two groups for onset of akinesia - analgesia is less than 30 s which was clinically negligible.

**Table 2**. Comparison of patient profile between Group 1 and Group 2.

| | Group 1 (without hyaluronidase) | Group 2 (with hyaluronidase) | P value (<0.05 significant) |
|---|---|---|---|
| N | 100 | 102 | 0.9 |
| Males | 41 | 43 | |
| Females | 59 | 59 | |
| Age: Mean | 58.6 years | 58.4 years | 0.8 |
| SD | 9.08 | 9.6 | |
| Min–Max | 40–81 years | 40–85 years | |
| Diabetics: N | 10 | 6 | 0.8 |
| Duration | | | |
| Mean | 4.2 years | 6 years | |
| Min–Max | 6 months–20 years | 2–14 years | |

**Table 3**. Comparision of requirement of augmentation of anaesthesia and surgical profile between Group 1 and Group 2.

| | Group 1 (without hyaluronidase) | Group 2 (with hyaluronidase) | P value |
|---|---|---|---|
| *Augmentaion of anaesthesia* | | | |
| Peribulbar | 7 | 2 | 0.3 |
| Subconjunctival | 2 | 3 | |
| *Duration of surgery* | | | |
| Mean | 30.6 min | 31.2 min | 0.5 |
| SD | 5.2 | 6.1 | |
| *Type of incision* | | | |
| Superior (N) | 98 | 101 | 0.6 |
| Temporal (N) | 2 | 1 | |
| *Intraoperative complications* | | | |
| Posterior capsule rent | 2 | 4 | 0.8 |
| Iridodialysis | 2 | 1 | |

Nine patients in Group 1 and five in Group 2 required augmentation of block in the form of peribulbar (n = 7 in Group 1; n = 2 in Group 2) or subconjunctival injections (n = 2 in Group 1; n = 3 in Group 2). However, no statistical difference was observed between the two groups with regards to supplemental anesthesia (p = 0.3), the duration of the surgery (p = 0.5) and intraoperative complications (p = 0.8). Also, the intraoperative complications were not attributable to the anesthesia solution (Table 3).

Eleven patients in group 1 and nine patients in group 2 had unsatisfactory akinesia graded as moderate movements or more by the operating surgeon. Of these, one patient from group 1 had no restriction of movements despite repeat peribulbar anesthesia. As the patient had adequate analgesia and was co-operative, surgery was successfully completed. Surgeon scoring with respect to akinesia, comfort/ease during surgery and orbicularis oculi action did not show significant difference by Mann Whitney U test (Graph 1).

15 patients gave pain score of 6 or more at the beginning of surgery (Group 1n = 7; Group 2n = 8). Only 1 patient (Group 1) gave a pain score of 6 at the end of surgery. The scores were similar in both groups (Graph 2).

## Discussion

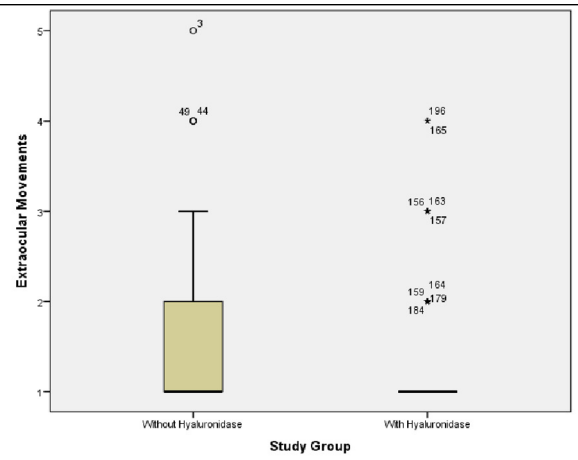
Hyaluronic Acid, a disaccharide polymer, is an important constituent of the extracellular matrix. Hyaluronidase promotes the diffusion of injected local anaesthetic agents through interstitial spaces by hydrolysing hyaluronic acid to tetrasaccharides and diminishing its normal high viscosity.[7] Combinations of hyaluronidase and local anesthesia have been used in the past with other regional blocks, but have lost popularity over a period of time.[8] Yet, hyaluronidase, continues to retain its place in ophthalmic anesthesia for over six decades.[4] Several workers have proposed different rationales justifying the inclusion of hyaluronidase in ophthalmic local anesthesia. These include, a smaller increase in intraocular pressure,[9] lesser distortion of the surgical site,[10] increased globe and lid akinesia and a decrease in postoperative strabismus.[11] Diversity in trial designs, anesthetic techniques, volumes and mixtures, measurement tools for akinesia and definition of a successful block has made a comparison amongst studies difficult.

The concentration gradient of the anesthetic agent is most important factor in the rate of diffusion of the agent.[12] Complete conduction blockade of all nerve fibers requires that an adequate volume and concentration of the local anesthesia be deposited. One of the supposed benefits of using hyaluronidase is that it would permit a smaller volume of local anesthesia in the peribulbar injection thereby minimizing an increase in the intraocular pressure.[13] While, authors have recommended volumes ranging from 5 to 8 ml as safe limits,[3,14] Dempsey et al. observed increased intraocular pressure in 4 out of 50 patients who were administered a peribulbar block of only 5 ml without hyaluronidase and attributed this to the predisposing smaller orbital volumes.[9]

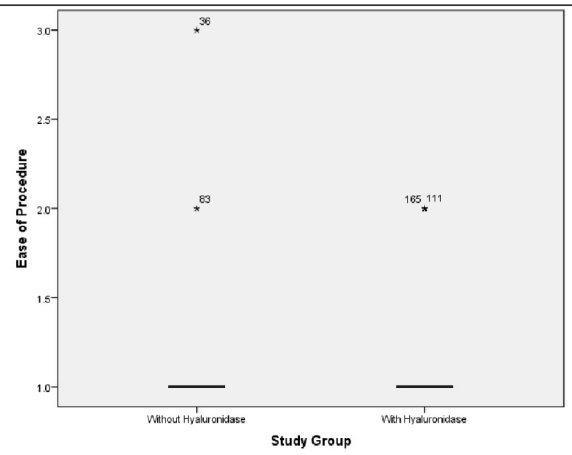
Yet there are quite a few studies in which anesthetic volumes are in excess of 10 ml even with hyaluronidase.[15,16] Most make no mention of the effect on intraocular pressure. Myelinated nerves need only 8–10 mm of the nerve length to be blocked to prevent saltatory conduction which can be achieved with volumes of local anesthesia that need not cause an increase in intraocular pressure.[12]

Hyaluronidase is also expected to hasten the onset of analgesia and akinesia, but studies have shown that the omission of this adjunct did not affect the quality of the peribulbar block.[10,14,16,17] The onset of anesthesia is dependent not only on the nerve diameter, but also on the pH of the anesthestic solution and tissue spaces into which it has been injected. Alkalinity increases the base form of the anesthetic agent which is more permeable across the nerve membrane.[12] Hyaluronidase renders the local anesthetic more alkaline. This may be more responsible for the rapid onset of akinesia/analgesia rather than its supposed role in disruption of tissue barriers. Epinephrine, on the other hand, reduces the pH of the solution, but this acidification does not significantly affect the onset of anesthesia.[12] Most clinical situations rarely require alteration of the pre-existing pH of the anesthesia solution as the vast buffering capacity of tissues tends to maintain a normal tissue pH.

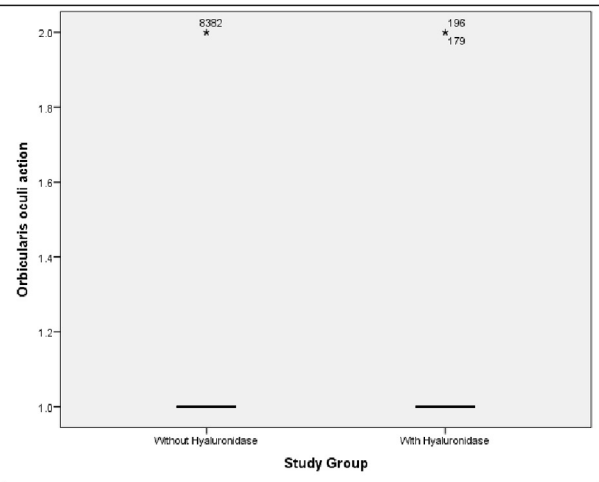
Of greater importance is the quality and duration of anesthesia to permit a comfortable surgery and pain free postoperative period. Hyaluronidase, by enhancing the uptake of local anesthesia would actually be decreasing the duration




1a: Box whisker plot comparing Surgeons' score of extraocular movements during surgery between Group 1 & 2.
Mann Whitney U test: U=4728.5; p=0.22.




1b: Box whisker plot comparing Surgeons' score for ease of procedure between Group 1 & 2.
Mann Whitney U test: U=5053.5; p=0.68.



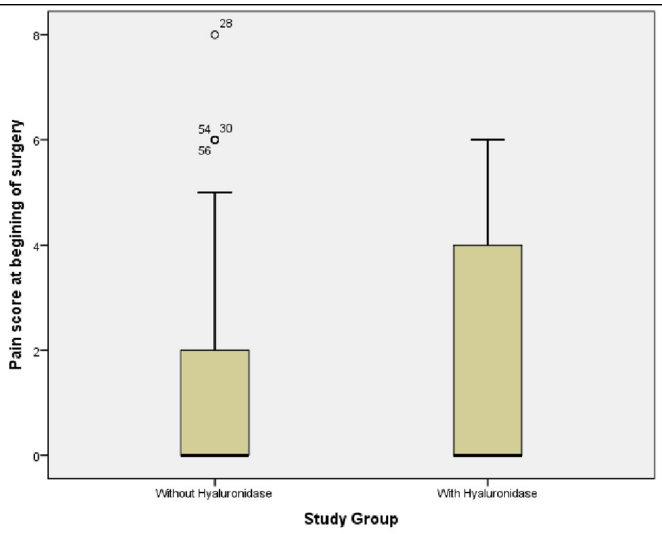

1c: Box whisker plot comparing Surgeons' score of orbicularis oculi block during surgery between Group 1 & 2.
Mann Whitney U test: U=5098.0; p=0.98.

**Graph 1.** Surgeons' score of akinesia.

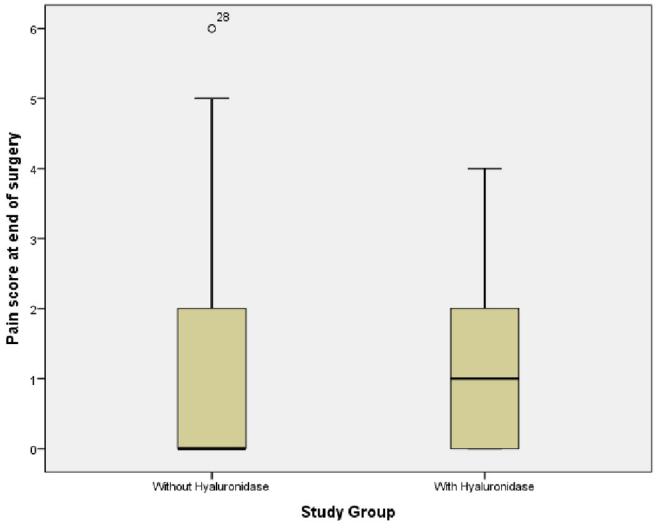
of the block and contribute to shorter pain free post-operative period.[18,19] Also, if entry of anesthesia solution into the orbital cavity is influenced by the action of hyaluronidase on the extracellular matrix, it is logical to expect at least some quantity of anesthesia to ''leak'' out back from the same pathways. The ocular massage performed after all peribulbar anesthesia injections may be responsible for preventing the ''expected backflow''. At best, the addition of hyaluronidase may be justified in situations where an ocular massage is contraindicated.

While a faster onset of akinesia and analgesia was observed with the use of hyaluronidase in this study, the difference between the two groups was not clinically significant. This negligible improvement cannot justify the addition of hyaluronidase even in busy camp settings. Further, the onset time of lignocaine (2–3 min) is more than sufficient in most clinical situations.[12]

There have been a few reports of post-operative strabismus following the use of hyaluronidase free local anesthesia. While the exact pathophysiology is unclear, the hypothesis is




2a: Box whisker plot comparing Patients' pain score at the beginning of surgery between Group 1 & 2. Mann Whitney U test: U=4803.5; p=0.44.




2b: Box whisker plot comparing Patients' pain score at the end of surgery between Group 1 & 2. Mann Whitney U test: U=4471.5; p=0.093.

**Graph 2.** Patients'score of analgesia.

that in the absence of hyaluronidase, the local anesthesia solution stagnates and remains in contact with the muscles for a longer period resulting in myotoxicity.[10,20] Studies examining this supposedly protective role of hyaluronidase gave conflicting results.[10,14,16,17]

Hamada et al. observed 27 cases of diplopia after peribulbar anesthesia in 7205 patients undergoing cataract surgery. All cases (0.75%) occurred after procedures in which peribulbar anesthetic solution did not contain hyaluronidase.[15] However, another group of ophthalmic surgeons compared the number of referred cases of post-operative diplopia from 7202 cataract surgeries during the times hyaluronidase was and was not available and observed no difference.[21] One group observed diplopia in three patients within one week of cataract surgery demonstrating a temporal association between the onset of diplopia and anesthesia injection.[22] However, information regarding the anesthetic agent used, exact technique, sites of injection, and the presence or absence of hyaluronidase was not available for any patient. As all three patients had a history of painful ocular injections, diplopia may be resultant to direct trauma to the extraocular muscle or inadvertent injection of the anesthetic solution into the muscle. A study determining the incidence of strabismus presenting after cataract surgery attributed nearly half of these to pre-existing or concurrent disorders masked by cataract. Further, surgical trauma from the anesthetic injection or the bridle suture appeared to be responsible in nearly 30% of cases.[23] The documented observation of post cataract diplopia with the use of topical anesthesia indicates that other factors must also be considered while evaluating post-operative diplopia.[24]

The clinical relevance of indirect chemical myotoxicity appears to be minimal as laboratory indicated that the damage was limited to only a thin rim of degenerated muscle fibres closest to the injection site. These changes were reversible with time, and the number of myofibrils affected was so small that no effect on the gross contractile properties of the muscle would be expected.[25]

A closer examination of some of the studies reporting diplopia revealed the total volume of the agent to be around of 10 ml. A lesser volume of anesthetic agent, even if injected close to muscle, may carry a lower risk of potential myotoxicity. Mahdy et al. found inferomedial block to be more effective and requiring only around 5 ml of anaesthetic agents.[6] In

the present study, a total volume of 5 ml of the local anesthetic agent was further divided into 3 ml and 2 ml in the inferomedial and superomedial quadrants respectively, thereby avoiding the concentration of large volume of the agent close to a single muscle. There were no cases of post-operative diplopia in either group.

The dose of hyaluronidase varies from 0.75 IU/ml to 300 IU/ml and despite such large variations, studies have failed to demonstrate any difference in the ocular anesthesia and concluded that there appears to be no clear dose–response relationship between hyaluronidase dose and the quality of the peribulbar block.[9,17]

Adverse events attributed to hyaluronidase include an increase in intraocular pressure, optic disc hemorrhage, exophthalmos, blindness and hypersensitivity reactions.[26,27] Hyaluronidase is believed to have a role in massive increase in capillary permeability seen in anaphylactic reactions and caution is advised in atopic individuals.[28] The destruction of orbital interstitial tissue barriers by hyaluronidase and the end products of hyaluron destruction may facilitate both the invasion and spread of the pathogens.[29] Further, animal derived hyaluronidase (the most commonly available) has been associated with low purity, variable potency and uncertain safety with a theoretical risk of spongiform encephalopathies.[30] The ophthalmic surgeon must also consider the added cost of hyaluronidase and the potential for human errors during its reconstitution.

There are a few shortcomings to this study. Firstly, only the time for onset of akinesia and analgesia was measured and no scoring of the extraocular muscle movement was performed. There is a pressure to perform the cataract surgeries received in response to rural screening programmes in the shortest possible time and we were unable to provide the time needed to score the extraocular movements in such a busy surgical unit. Secondly, while the adequacy of analgesia was measurable with the recti bridal suturing, the adequacy of akinesia graded by the ophthalmic surgeon was subjective and dependent on the individual surgeon's comfort to work with incomplete akinesia. Thirdly, only cases scheduled to be performed by qualified ophthalmologists were included in this study. We felt that since the effect of withholding of hyaluronidase in anesthesia is being evaluated, trainee surgeons working at a slower pace may find it difficult if either the akinesia is incomplete or the anesthesia wears off before the surgery is completed.

## Conclusion

Deposition of the anesthesia as close as possible to the target nerve, smaller volumes and adequate induction time with ocular compression would facilitate a successful block within a few minutes in most cases.[12] In this study, the addition of hyaluronidase conferred no benefit to the efficacy of the peribulbar anesthesia. In view of the above result and the added risks of potential allergies and errors in reconstitution, we recommend that the addition of hyaluronidase is not needed for peribulbar anesthesia in cataract surgery.

## Conflict of interest

The authors declared that there is no conflict of interest.

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