Hyaluronidase reduces local anaesthetic volumes for sub-Tenon’s anaesthesia

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Background. Volumes of local anaesthetics for sub-Tenon’s anaesthesia vary. Lower volumes produce less akinesia, whereas higher volumes increase chemosis and intra-ocular pressures. Hyaluronidase is often added to local anaesthetics to improve akinesia without increasing the volume of the injection, but this is controversial. This randomized, sequential allocation study examines the addition of hyaluronidase on the minimum local anaesthetic volume (MLAV) required for a sub-Tenon’s block.

Methods. Sixty-two patients having sub-Tenon’s blocks for cataract surgery were randomized into two groups. The control group (n=31) received 2% w/v lidocaine and the study group (n=31) received 2% w/v lidocaine with hyaluronidase 15 IU ml–1. Using parallel up–down sequential allocation from a 4 ml starting volume, the volumes in both groups were changed using a testing interval of 1 ml according to the quality of globe akinesia. The median effective local anaesthetic volume (MLAV) was calculated for both groups using probit regression.

Results. The groups were similar for age, sex, and ocular axial length. The MLAV in the hyaluronidase group was 2.6 ml [95% confidence interval (CI), 2.1–3.1] and 6.4 ml (95% CI, 5.1–8.1) in the control group (P<0.002).

Conclusions. Hyaluronidase permits a significant 2.4-fold (95% CI, 1.8–3.4) reduction in MLAV for sub-Tenon’s anaesthesia.


Keywords: anaesthetic techniques, regional, sub-Tenon; drug delivery, volume; enzymes, hyaluronidase; eye, cataract

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Sub-Tenon’s block is a popular technique for ophthalmic local anaesthesia, affording good quality analgesia and ocular akinesia.1 2 It involves the use of a blunt rather than sharp needle, so the risks of globe perforation and brain-stem anaesthesia are reduced but not entirely eliminated.3 4 The most common complications are conjunctival haemorrhage and chemosis.3 4 The latter can make surgical access more difficult and may interfere with formation of the scleral flap in glaucoma surgery.5 It can be minimized by reducing the volume of injected local anaesthetic. However, reductions in the volume of local anaesthetic are associated with deteriorations in analgesia and extra-ocular muscle akinesia, which may make surgery more difficult. The addition of hyaluronidase, which hydrolyses part of the intracellular matrix that maintains tissue integrity, allowing the local anaesthetic to disperse more extensively around the orbit, may allow smaller volumes to be given. This could lead to a reduction in complications without loss of efficacy.

Conventional studies using fixed volumes of local anaesthetic solution have failed to confirm the benefits of hyaluronidase.6–20 Reasons for this include uncertainty about the optimum hyaluronidase concentration, pH variability of local anaesthetic solutions, effect of added vasoconstrictors,
and differing properties of individual local anaesthetics. A variable that has not been studied is the effect of volume. We used a minimum local anaesthetic volume (MLAV) study design, with up–down sequential allocation, to evaluate whether hyaluronidase permits a reduction in volume of local anaesthetic in sub-Tenon’s anaesthesia. The primary outcome was to estimate the MLAV causing akinesia and the secondary outcome was to assess the degree of chemosis related to the volume of injection.

Methods
After local ethics committee and Medicines and Healthcare products Regulatory Agency (MHRA) approval, American Society of Anesthesiologists physical status (ASA PS) class I–III patients, undergoing elective day case cataract surgery under local anaesthesia, were recruited into this randomized prospective double-blind study. Those with allergies to local anaesthetics or hyaluronidase, previous eye surgery, pre-existing extra-ocular muscle palsies, or communication difficulties were excluded from the study. After informed consent had been obtained, participants were allocated according to a computer-generated random number order into two groups. Group H received a sub-Tenon injection with lidocaine 2% w/v with hyaluronidase 15 IU ml⁻¹, whereas Group C received plain lidocaine 2% w/v. An up–down sequential allocation technique was used, starting with an arbitrary volume of 4 ml of local anaesthetic solution. Subsequent volumes of local anaesthetic were dependent on the response of the previous patient in that group using a testing interval of 1 ml. An investigator (H.S.), who had no clinical role in the study, randomized the patients into two groups and prepared the local anaesthetic syringes immediately before surgery. The solutions were prepared in 10 ml syringes with labels to obscure the exact volume of local anaesthetic in the syringe.

In the anaesthetic room, monitoring included ECG, pulse oximetry, and non-invasive arterial pressure. No sedation was used. Topical conjunctival anaesthesia was achieved with drops of proxymetacaine 0.5% w/v followed by tetracaine 1% w/v. The conjunctiva and surrounding skin were cleansed using an aqueous iodine solution. All sub-Tenon’s blocks used the inferonasal route and were performed by one experienced investigator (H.A.M.), using a 19 G Visitec sub-Tenon cannula.

After the sub-Tenon’s injection, digital pressure was applied to the closed eye for 5 min, then globe akinesia was assessed by another investigator (M.D.), who was blinded to the syringe contents. The system used to score akinesia was that described by Bramha, in which globe movement was scored from three to zero in each of the secondary directions of gaze (abduction, adduction, depression, and elevation). Three to zero represent from full movement through partial and flicker of movement to no movement. A fully mobile eye scored 12, whereas an immobile eye scored zero. If the akinesia score was four or less, the block was deemed effective and the following patient randomized to that group received a reduction of 1 ml of local anaesthetic solution. If the akinesia score was five or more, the block was deemed ineffective and the next patient received 1 ml more local anaesthetic. If the score was greater than eight, the patient received a top-up sub-Tenon’s injection of 3 ml of lidocaine 2% w/v. At the onset of the study, a lower limit of 1 ml and an upper limit of 10 ml were agreed with the investigators. At these limits, the same volume was repeated as appropriate for the next patient randomized to that group. Similarly, where breaches in the protocol occurred the patient was withdrawn and that volume repeated for the next patient randomized to the same group.

Chemosis was assessed by counting the number of quadrants affected. Patients were asked to rate injection pain using a verbal response scale from 0 (no pain) to 10 (worst imaginable pain). Age, ASA PS, gender, axial length of the eye, and duration of surgery were recorded. Side-effects of hyaluronidase and the requirement for supplemental analgesia (amethocaine drops used by the surgeon) were also noted.

A power analysis indicated that 49 subjects would be required per group to detect a difference of 25% (1 ml) in the volume used, with a power of 0.80 and significance at 0.05 for the primary outcome. An aggregate of the standard deviation (1.75 ml) was taken from published studies on peribulbar anaesthesia. The sequences were analysed using probit regression to estimate the median effective volume (EV₅₀), which was defined as the MLAV. Probit regression was also used to estimate the probabilities of success for the volumes studied. Spearman (rₛ) correlation coefficients were used to compare chemosis and volume relationships. Analyses were performed using the following software: Excel 2000 (Microsoft Inc., Redmond, WA, USA) and Minitab 14.2 (Minitab Inc., State College, PA, USA). Significance was defined at P<0.05 (two-sided).

Results
The study was halted after 62 patients were recruited. There were no protocol violations.

The groups were similar in respect of patient characteristics, axial length, duration of surgery, and pain scores (Table 1). Using probit regression, the median effective volume (EV₅₀) for a sub-Tenon’s block to produce sufficient akinesia of the eye was 2.6 ml [95% confidence interval 2.3–2.9] for Group H, compared with 3.1 ml [2.8–3.4] for Group C. The chemosis was assessed by counting the number of quadrants affected. There was no statistically significant difference between the groups (Table 1).

To further investigate differences in chemosis, the proportion of patients with chemosis was compared. There was a significant difference between the groups (Table 1). The number of patients with chemosis was higher in Group H (41%) compared with Group C (29%).

Table 1 Patient characteristics. Results are mean [range], ratio or mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Hyaluronidase group (n=31)</th>
<th>Control group (n=31)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>69 [50–90]</td>
<td>77 [53–98]</td>
</tr>
<tr>
<td>ASA PS</td>
<td>II [1–III]</td>
<td>II [1–III]</td>
</tr>
<tr>
<td>Gender</td>
<td>M:F 14:17</td>
<td>M:F 9:22</td>
</tr>
<tr>
<td>Axial length (mm)</td>
<td>23.6 (1.2)</td>
<td>23.4 (1.3)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>29 (5.8)</td>
<td>28 (11.1)</td>
</tr>
<tr>
<td>VRS pain score</td>
<td>1 [0–4]</td>
<td>1 [0–7]</td>
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interval (CI), 2.1–3.3] in Group H and 6.4 ml (95% CI, 5.1–8.1) in Group C. The ratio between these volumes was 2.4 (95% CI, 1.8–3.4), \( P < 0.002 \) (Table 2). The results of the effective and ineffective outcomes for both groups are shown with 95% CI in Figure 1. The probability of success curve (Fig. 2) further demonstrates the difference between the groups. Group H showed significantly less variability (\( P = 0.01 \)).

There was a significant positive correlation for volume injected and chemosis score (\( r_s = 0.69, P < 0.0001 \)). On assessment of akinesia, nine patients scored >8 (Group H: 7 and Group C: 2) and required a supplemental sub-Tenon’s injection before surgery (NS). Topical rescue analgesia was required by three and two patients in Groups H and C, respectively (NS). No adverse effects to hyaluronidase were noted and no patients came to any harm.

**Discussion**

This study achieved its aim and showed that the addition of hyaluronidase 15 IU ml\(^{-1}\) to lidocaine 2% w/v allowed a significant reduction in volume from 6.4 to 2.6 ml. The clinical benefits of the reduction in volume are evident from the positive correlation between volume of local anaesthetic and chemosis score. The study also shows that the addition of hyaluronidase significantly reduces variability. The clinical benefits of this should be apparent in the improved predictability of achieving satisfactory akinesia with a given volume of local anaesthetic. This is a new finding.

The number of subjects in our study was smaller than originally planned. Before the study was complete, the Ophthalmic Day Unit underwent a service reconfiguration resulting in organizational difficulties that prevented the study from continuing. At this point, 62 patients had been recruited and a decision was made to preview the results. It then became clear that the effect size due to the addition of hyaluronidase had been underestimated; hence, the actual difference in volumes between the two groups was much greater than anticipated.

The predefined upper and lower limits for local anaesthetic volumes set for this study did not have an evidence basis, but were largely determined by the clinical experience of one of the investigators (H.A.M.). During the study, the blinded investigator found that one of the injected volumes (8 ml) had produced an unacceptable increase in intra-ocular pressure, as observed from digital palpation. As the volumes were obscured, and although the investigator was unaware that 9 ml had already been used in the study, after review it was decided to reset the upper limit to 8 ml for the remainder of the study. This upper limit operated twice in the control group. Without this protocol amendment, we would expect to find the control group to have greater variability, a larger difference in groups and a further underestimation of the true effect size. Despite the attempts to obscure the volume markings on the syringes and blinding the operator to the group allocation and sequence position, the plunger depths would have been sufficiently different between the groups to possibly allow identification. The scale of the difference was not anticipated and we had not predicted that

<table>
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<tr>
<th>Estimate</th>
<th>95% CI</th>
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<tr>
<td>Control (ml)</td>
<td>6.4</td>
</tr>
<tr>
<td>Hyaluronidase (ml)</td>
<td>2.6</td>
</tr>
<tr>
<td>Ratio</td>
<td>2.4</td>
</tr>
<tr>
<td>( P )-value</td>
<td>0.002 *</td>
</tr>
</tbody>
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**Table 2** Median effective volumes, ratio and 95% confidence intervals (95% CI)

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Fig 1 Effective/ineffective volume sequences for C: Group C (lidocaine 2% w/v) and H: Group H (lidocaine 2% w/v with hyaluronidase 15 IU ml\(^{-1}\)). Horizontal lines represent EV\(_{50}\)'s with 95% confidence intervals.

Fig 2 Probability of success plot.
this might be a problem. However, all primary and secondary outcomes (akinesia and chemosis) were determined by a third investigator (M.D.) who was blinded to group allocation and syringe volumes.

No comparative data on the volume effect of hyaluronidase exist in the current literature. Hyaluronidase has been shown to improve ocular akinesia and time of onset in eight studies of either retrobulbar, peribulbar, or sub-Tenon’s anaesthesia. Another four studies of peribulbar anaesthesia have failed to show an effect. A review of these studies shows that where hyaluronidase was found to be effective, a smaller volume was used typically 5–8 ml. Where a larger volume was used (8–11 ml), the hyaluronidase appeared to contribute little to the block in terms of akinesia. If the orbit is already relatively full of local anaesthetic, the additional, and probably marginal, effect of hyaluronidase is not apparent. In contrast, when a small volume of local anaesthetic is used, the improvement with hyaluronidase is revealed.

The sequential allocation design has been criticized as it identifies the EV 50 rather than the more clinically useful EV 95 used in conventional studies. The sequential allocation design concentrates the data points around the steep part of the volume-response curve where changes in volume estimates are minimized, it is more robust than at EV 95 where both precision is reduced and errors can possibly exaggerate any differences that are found.

The aim of this study was to demonstrate the effect on volume when hyaluronidase was added to the local anaesthetic solution by testing volumes about the EV 50 and not to estimate the EV 95. Although this study was not intended to directly estimate the volumes required for clinical efficacy, it does provide us with insight into the magnitude of the likely effectiveness of hyaluronidase in this setting. In conclusion, we have shown, using this sequential allocation model that the addition of hyaluronidase significantly reduces, by a factor of 2.4, the volume of local anaesthetic that is required for a satisfactory surgical field with reduced chemosis.

Acknowledgements

The authors thank Margaret Dutton (ODP in the Ophthalmic Day Surgery Unit, St James’s Hospital, Leeds) for her involvement and diligence in performing the akinesia and chemosis scores.

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