Re-evaluation of hyaluronidase in peribulbar anaesthesia

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Abstract

***Aims/background*—Hyaluronidase can augment the actions of local anaesthetics in peribulbar anaesthesia. However, evidence suggests satisfactory anaesthesia can be achieved using mixtures without hyaluronidase. A randomised double blind study was conducted on 50 patients, undergoing peribulbar anaesthesia, to validate this observation.**

***Methods*—Patients received a standard mixture of local anaesthetic (0.5% bupivacaine and 2% lignocaine in a 1:1 ratio) with or without hyaluronidase (25 IU/ml of mixture), pH values 5.16 and 5.24 respectively. Time taken to establish satisfactory anaesthesia to allow surgery was noted.**

***Results*—The onset time to globe akinesia in the control group ranged from 2 to 15 minutes (mean 5.64 and median 4 minutes) and in the hyaluronidase group from 2 to 12 minutes (mean 4.64 and median 4 minutes). The volume of local anaesthetic injected to achieve satisfactory anaesthesia ranged from 8 to 16 ml (mean 10.96, SD 1.95) in the control group and 10 to 18 ml (mean 11.64, SD 2.8) in the hyaluronidase group. A Mann–Whitney test to compare onset times to globe akinesia between groups gave a p value = 0.6 and 95% confidence interval (-1 to 2 minutes).**

***Conclusion*—Addition of 25 IU/ml of hyaluronidase to a standard pH unadjusted local anaesthetic mixture does not significantly reduce the time to the onset of satisfactory globe akinesia.**

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Hyaluronidase is a preparation of purified ovine testicular protein enzyme. Its action is to depolymerise and hydrolyse hyaluronic acid, a glycosaminoglycan which normally obstructs intercellular diffusion by binding cells together in a 'jelly-like' matrix.[1] It has been proposed that hyaluronidase increases the permeability of the fibrous septa that compartmentalise the orbital contents, thereby enhancing the uniform spread of local anaesthetic.[2] This not only improves the speed of onset and quality of nerve block, but also serves to reduce the increase in intraocular pressure sometimes seen after peribulbar block. Hyaluronidase was first reported to augment the spread of local anaesthetic solutions in peribulbar anaesthesia in 1986[3] and has subsequently achieved widespread acceptance in clinical practice. Further studies have endorsed the 'synergistic effects' of using combinations of hyaluronidase with local anaesthetic solutions to hasten the onset of peribulbar anaesthesia.[4]

The temporary unavailability of the UK manufactured commercial product 'Hyalase' (CP Pharmaceuticals Ltd, Wrexham, Clwyd) in the early 1990s, coupled with the nationwide shortage of the American imported product 'Wydase' (Wyeth), led the authors to the opinion that satisfactory peribulbar anaesthesia could be achieved, with no apparent delay in onset or quality of block, without the addition of hyaluronidase.

In view of the fact that hyaluronidase is associated with a low but appreciable incidence of potentially serious allergic reactions,[5,6] we conducted a double blind randomised study to investigate our provisional findings.

Patients and methods

Ethics committee approval was granted and informed consent given by 50 patients, age range 33 to 91 years, scheduled to undergo peribulbar anaesthesia for cataract extraction and lens implantation. Patients with a history of local anaesthetic complications, or who were currently taking anticoagulants, were excluded. Each of the patients was randomly allocated to one of two groups, using a random figure table and sealed envelope system. Those patients in group C (control group) received a standard local anaesthetic mixture containing plain 2% lignocaine and 0.5% bupivacaine in a 1:1 ratio. Those in group H (hyaluronidase) received the same local anaesthetic mixture with the addition of Hyalase made up to a concentration of 25 international units (IU) of hyaluronidase per millilitre of the local anaesthetic mixture. On arrival in the anaesthetic room intravenous access and non-invasive monitoring were established (blood pressure, ECG, and pulse oximetry), before instilling two drops of 0.4% oxybuprocaine into the eye. Syringes containing the local anaesthetic mixtures were prepared freshly before each theatre session by an anaesthetist who played no further part in the patients' management. Syringes were uniquely identified with a code number matched to the anaesthetist's patient assessment sheet. The contents of each syringe and patient details were recorded in a booklet kept in the theatre suite and only made available to the attending anaesthetist in the event of an emergency. All blocks were performed and assessed by one consultant anaesthetist, experienced in the technique of peribulbar anaesthesia as described by Fry and Henderson,[7] and all surgery performed by one consultant surgeon. A Honan ocupression device was applied to the eye after the completion of the

block and assessments of globe and lid akinesia were performed at 1 minute intervals until satisfactory akinesia, such that surgery could be performed, was achieved.

A three category classification for akinesia was used to simplify the interpretation of the results. Akinesia was scored as follows:

1 = total akinesia—no movement in any plane,

2 = satisfactory akinesia—less than 2 mm of movement in any direction, not warranting further action before surgery could commence, and

3 = unsatisfactory akinesia—greater than 2 mm of movement in any one or more direction warranting further supplemental injections.

If the akinesia score remained at 3 at 5 minutes then a further 3–4 ml of the mixture was administered, the inferior injection repeated for inferolateral movements, the superior for superomedial movements, or both where necessary. Patients were questioned directly about pain associated with the peribulbar injection and their overall satisfaction with the procedure.

These comments were noted, along with any made by the surgeon or anaesthetist, and recorded on the patient assessment sheet (available on request to interested readers).

STATISTICAL METHODS

Based on the findings of a pilot study, estimating standard deviation = 5.5 minutes and assuming a 5 minute difference between groups to the onset of globe akinesia to be medically significant, then using Altman's nomogram, we estimated the number of patients needed in each study group to equal 25 (p = 0.05 and power = 0.9).

A Mann–Whitney test was used to compare the onset times to globe akinesia between groups (positively skewed distribution of data, see Fig 1) and an unpaired Student's *t* test to compare the volumes of local anaesthetic injected in each group.

Results

The two groups were comparable in terms of age, ASA grade, and sex distribution (Table 1).

Unintentionally, all but one patient were male. Onset time to globe akinesia in group C ranged from 2 to 15 minutes (mean 5.6, median 4.0 minutes); and in group H from 2 to 12 minutes (mean 4.2, median 4.0 minutes), 95% confidence interval (-1 to 2), p value 0.6 (Fig 1).

In all but one case in group H, where the time taken approached 30 minutes and the total injected volume was 18 ml, satisfactory conditions were achieved such that surgery could be performed within 15 minutes of the completion of the block, with mean injected volumes for groups C and H of 10.6 (SD 2.2) and 11.6 (2.7) ml, respectively, 95% confidence interval (-0.7–2.1), p value 0.32 (Table 2).

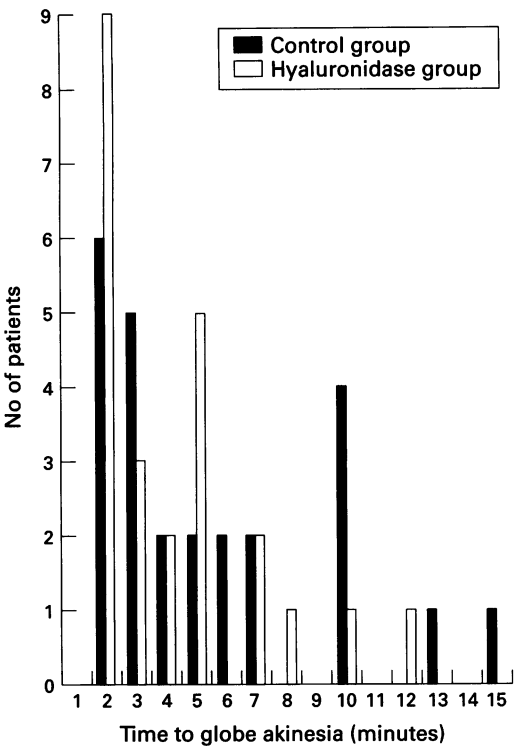

Figure 1 Onset time to globe akinesia.

Neither the difference in time to onset of block, nor the volume injected in either group to achieve anaesthesia were statistically significant. All but three patients in the control group C complained of pain associated with the peribulbar injection of local anaesthetic and not the initial skin infiltration. Only one patient in the hyaluronidase group was dissatisfied with the outcome of the block. He required three additional injections, two superior and one inferior, before satisfactory anaesthesia and operating conditions could be achieved.

In group C 17 patients had total akinesia and seven satisfactory akinesia at the onset of surgery, with seven patients requiring a supplemental injection at 5 minutes (as described).

Of these, 22 blocks were graded 'good' and two 'satisfactory' by the surgeon. In the one block deemed 'unsatisfactory' by the surgeon there remained a degree of superior rectus movement despite a further injection.

Table 1 Patient characteristics—age, sex, and ASA distribution

	Group C (n=25) (control)	*Group H (n=25) (hyaluronidase)*
Age (years) range	33 to 85	59 to 91
Mean (SD)	67 (12)	71 (9)
Male/female	24/1	25/0
ASA		
1	13	9
2	11	12
3	1	3
4	0	1

Table 2 Injected volumes and time to onset of globe akinesia

	Group C (control)	*Group H (hyaluronidase)*
Injected volume (ml)		
Range	8 to 16	10 to 18
Mean (SD)	10.6 (2.2)	11.6 (2.7)
Onset time to globe akinesia (min)		
Range	2 to 15	2 to 12
Mean, median (SD)	5.6, 4.0 (3.7)	4.2, 4.0 (2.8)

Nevertheless, surgery was completed painlessly, which serves to illustrate the point that the onset times of motor (akinesia) and sensory (anaesthesia) blockade are not always matched. In group H 16 patients had total and eight satisfactory akinesia, with nine patients requiring a further supplement to the initial block at 5 minutes. In this group, 21 were graded 'good' and three 'satisfactory'. One block was deemed 'unsatisfactory' because of persistently elevated intraocular pressure, such that a lens could not be implanted after cataract extraction (10 ml of local anaesthetic was injected in this case). There was no evidence of an inadvertent intraocular injection or orbital haemorrhage to account for this and the cause remained undetermined.

Discussion

This study failed to demonstrate a statistically significant difference in (a) the time to onset of satisfactory globe akinesia and (b) the volume of local anaesthetic injected, in two groups of patients receiving a mixture of pH unadjusted plain lignocaine and bupivacaine with or without the addition of hyaluronidase 25 IU/ml, pH values 5.24 and 5.16, respectively. These findings are supported by the work of Crawford and Kerr[8] who, although making no comment on the speed of onset of globe akinesia, reported similar mean (SD) injected volumes of 8.9 (2.6) ml and 9.0 (1.8) ml in pH unadjusted local anaesthetic mixtures with and without hyaluronidase, respectively.

Only two blocks in our study were judged to be unsatisfactory by the operating surgeon. In one patient, in the control group, superior rectus movement persisted despite further injection and in one patient in the hyaluronidase group a raised intraocular pressure prevented lens insertion. This finding, in contrast with those of Zahl *et al*[9] and Lewis *et al*[10] who reported unsatisfactory 'failure rates' of 9/26 and 5/17 respectively in their patient groups receiving plain local anaesthetic, may be due to the fact that anything less than total akinesia was classified by these authors as a 'failure'. Roberts *et al*[11] similarly reported a failure rate approaching 50% within 30 minutes of injection, but pointed out that many of these so called 'failed blocks' demonstrated only residual movements of the globe, the nature of which would be unlikely to interfere with surgery.

The exact role of hyaluronidase in peribulbar anaesthesia has yet to be fully agreed. Despite initial studies advocating its use, claiming a more rapid onset and improved quality of block, more recent publications have begun to question its value.

Morsman *et al*[2] found that hyaluronidase had a substantial beneficial effect, when added to a plain local anaesthetic mixture, doubling the proportion of those attaining 'good anaesthesia' from 33% without to 69% with its addition. The authors point out that this was a 'non-blinded' observation and therefore, we feel, caution should be exercised when interpreting these results. Davis and Mandel reported a 90% success rate in achieving complete anaesthesia within 10 minutes of using a lignocaine and hyaluronidase solution[3] and House *et al* found that both adrenaline and hyaluronidase were 'vital for satisfactory anaesthesia'.[4] It is worthy of note that in the latter study the authors only used one tenth of the dose of hyaluronidase conventionally described in the literature and gathered data on numerous small groups which confounded the interpretation of the results.

In contrast, Roberts *et al*[11] reported the efficacy of a pH unadjusted lignocaine, bupivacaine, and hyaluronidase mixture to be equal to or lower than that of a solution without hyaluronidase adjusted to the same pH of 5. Taking into consideration that the pH limits of activity for hyaluronidase are 6.4 to 7.4 (Wyeth Ltd, Berks), one would expect it to have limited enzymatic activity in an environment outside this pH range. This is borne out in the findings of Barr *et al*[12] who demonstrated that the addition of hyaluronidase to a plain (pH unadjusted) mixture did not increase the rate of absorption of local anaesthetic. One could have reasonably expected the absorption to have increased if the hyaluronidase present was being effective in promoting spread of local anaesthetic. This supports both our study findings and those of Crawford and Kerr and leads us to the conclusion that there is little, if anything, to be gained from the addition of hyaluronidase to plain, pH unadjusted, local anaesthetic mixtures.

There are inherent risks associated with the use of hyaluronidase.[5,6] Not only have there been cases of allergic reaction reported following its use, but also it is itself now implicated in the mechanism of action of the massive increase in capillary permeability seen in anaphylaxis and therefore caution is advised with its use in atopic individuals.[1]

We feel that with our current practice, rapid and effective peribulbar anaesthesia can be reliably achieved, to the satisfaction of the surgeon, without the need to add hyaluronidase to the local anaesthetic mixture.

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