IS HYALURONIDASE HELPFUL FOR PERIBULBAR ANAESTHESIA?

R. J. C. BOWMAN, D. K. NEWMAN, E. C. RICHARDSON, A. B. CALLEAR and
D. W. FLANAGAN

Huntingdon

SUMMARY

A prospective, randomised controlled study was performed to investigate whether hyaluronidase improved the efficacy of peribulbar anaesthesia. Ninety-two patients undergoing peribulbar anaesthesia for intraocular surgery all received 10 ml of an anaesthetic solution consisting of a 50:50 mixture of 2% lignocaine with 1 in 200 000 adrenaline and 0.5% bupivacaine. Patients were randomised to a hyaluronidase group which received 150 IU/ml hyaluronidase in this anaesthetic solution (a higher concentration than previous studies) or a control group which received no hyaluronidase. There were 44 patients in the hyaluronidase group and 48 patients in the control group. All anaesthetic injections were administered by an experienced ophthalmologist and no supplementary injections were required in any case. The mean time interval between administration of the block and commencement of surgery was 22 minutes. No statistically significant difference was found between the two groups for pre-operative akinesia ($p = 0.16$), intra-operative akinesia ($p = 0.25$), eyelid paralysis ($p = 0.72$), objective analgesia ($p = 0.23$) or subjective analgesia ($p = 0.60$). The majority of patients in both groups achieved excellent akinesia, eyelid paralysis and analgesia. The reasons for these findings in the light of previously conflicting reports on the value of hyaluronidase in peribulbar anaesthesia are discussed.

Peribulbar anaesthesia is a widely used local anaesthetic technique for eye surgery in the United Kingdom. It has largely replaced the retrobulbar block, having reduced the risk of serious complications (inadvertent globe perforation and retrobulbar haemorrhage).¹ However in a peribulbar block the anaesthetic solution is injected well away from its site of action – the nerves which lie within the extraocular

muscle cone. The anaesthetic agents therefore have to diffuse through the orbital tissues in order to exert their effect. The addition of hyaluronidase to the anaesthetic solution was advocated by early proponents of the technique.² Hyaluronidase is an enzyme which catalyses the depolymerisation of hyaluronic acid to a tetrasaccharide. It is thought to improve the efficacy of local anaesthetic injections by breaking down the interstitial cell barrier thereby facilitating diffusion of the anaesthetic agent. The value of hyaluronidase in improving the efficacy of peribulbar blocks has yet to be convincingly demonstrated. Reports of its efficacy vary considerably.^{3–7} To date there has been only one randomised controlled trial of hyaluronidase employed in conjunction with the commonly used anaesthetic agents.³ This study found no benefit from its use but only involved 60 patients and may not have had sufficient power to detect a small benefit from hyaluronidase. Certainly the enzyme remains in common use and we have therefore conducted a double-masked randomised controlled study on a larger number of patients to determine whether there is any evidence to support the routine use of hyaluronidase for peribulbar anaesthesia.

PATIENTS AND METHODS

Ninety-two consecutive patients undergoing peribulbar anaesthesia for elective intraocular surgery (extracapsular cataract extraction, phacoemulsification and trabeculectomy) were enrolled in the study. Informed consent was obtained from each patient.

The peribulbar block was administered in a standard way to every patient by an experienced ophthalmologist. The local anaesthetic solution consisted of a 50:50 mixture of 2% lignocaine with 1 in 200 000 adrenaline and 0.5% bupivacaine. Patients were randomly allocated to receive 150 IU/ml hyaluronidase (hyaluronidase group) or no hyaluronidase (control group) in this anaesthetic solution.

From: Hinchingsbrooke Hospital, Huntingdon, Cambridgeshire, UK.

Correspondence to: R. J. C. Bowman, FRCOphth, Tennent Institute of Ophthalmology, Western Infirmary, Glasgow, G11 6NT, UK.

Table I. Distribution of patients in the hyaluronidase and control groups

	Hyaluronidase group (<i>n</i> = 44)	Control group (<i>n</i> = 48)
Mean (SD) age (years)	72.0 (11.5)	75.0 (8.6)
Gender profile	16 M / 28 F	17 M / 31 F
No. of patients with previous intraocular surgery under local anaesthesia	12	16
Patients with diabetes mellitus	4	6
Mean (SD) anaesthetic interval (min)	22.4 (1.7)	21.3 (1.5)
Mean (SD) duration of surgery (min)	32.7 (2.2)	35.9 (2.4)
Type of operation		
ECCE + IOL	27	30
Phacoemulsification + IOL	13	14
Trabeculectomy	4	4

ECCE, extracapsular cataract extraction; IOL, intraocular lens. There is no statistically significant difference between the two groups for any parameter (Student's two-tailed *t*-test or χ^2 test, *p* > 0.05).

After the conjunctiva had been anaesthetised with topical amethocaine 1%, the peribulbar injection was given using a 25 gauge 25 mm needle. A total of 10 ml of the anaesthetic solution was given, with 5 ml being injected into the inferotemporal orbit by a transconjunctival route and 5 ml being injected into the medial orbit via the caruncle. A Honan's ocular compression balloon was applied to the eye and inflated to a pressure of 30 mmHg. The balloon was left *in situ* until the commencement of surgery (at least 10 minutes). The anaesthetic interval and duration of surgery were recorded for each patient. A superior rectus bridle suture was applied only if akinesia was judged insufficient by the surgeon, except in trabeculectomies, for which it was routinely employed.

The following were assessed for each patient: pre-operative akinesia, intra-operative akinesia, intra-operative eyelid movement, objective analgesia (assessed by the surgeon) and subjective analgesia (assessed by the patient shortly after completion of surgery). The study was masked: neither the patient nor the assessor knew to which group the patient belonged. The assessments were made by a single surgeon (D.W.F.). Ocular and eyelid movement were both assessed using a visual analogue scale from 0 to 10, with 0 representing no movement and 10 representing full movement. In an attempt to

establish whether hyaluronidase had helped the anaesthetic spread to any particular motor nerve, pre-operative ocular movement was also assessed separately for globe elevation, depression, abduction and adduction. Analgesia was similarly assessed using a visual analogue scale from 0 to 10, with 0 representing no pain and 10 representing the worst pain the assessor (surgeon or patient) could imagine. Statistical analysis was performed using a Student's two-tailed *t*-test or the chi-squared test as appropriate.

RESULTS

The hyaluronidase group contained 44 patients and the control group 48 patients. Table I shows that the two groups were matched for age, sex, previous intraocular surgery under local anaesthesia, diabetes mellitus, anaesthetic interval, duration of surgery and type of operation. No patient in either group required an additional anaesthetic injection before or during surgery. Since the majority of patients in each group had achieved complete akinesia and analgesia, the visual analogue data was stratified into those with complete versus incomplete analgesia and akinesia to allow statistical analysis. There was no statistically significant difference between the two groups regarding the proportion of patients achieving complete pre-operative akinesia, intra-operative akinesia, objective analgesia or subjective analgesia (Table II). Intra-operative eyelid movement was uncommon, with no statistically significant difference between the two groups (Table II).

There was no statistically significant difference in the proportion of patients in each group achieving complete block of elevation ($\chi^2 = 0.052$, *p* = 0.82), depression ($\chi^2 = 0.536$, *p* = 0.46), abduction ($\chi^2 = 0.010$, *p* = 0.92) or adduction ($\chi^2 = 1.919$, *p* = 0.18). Concerning superior rectus bridle sutures there were no statistically significant differences between the two groups either in the proportions of patients undergoing cataract surgery who required them (2 of the hyaluronidase group and 3 of the control group: $\chi^2 = 0.004$, *p* = 0.95) or in the proportions of patients (undergoing cataract or trabeculectomy) experiencing pain on application of the suture (1 of the hyaluronidase group and 3 of the control group: $\chi^2 = 1.040$, *p* = 0.31).

Table II. Effect of hyaluronidase

	No. (%) patients in hyaluronidase group (<i>n</i> = 44)	No. (%) patients in control group (<i>n</i> = 48)	χ^2 test, d.f. = 1 (<i>p</i> value)
Complete pre-operative akinesia	26 (59.1)	35 (72.9)	1.96 (<i>p</i> = 0.16)
Complete intra-operative akinesia	38 (86.4)	37 (77.1)	1.31 (<i>p</i> = 0.25)
Absent intra-operative eyelid movement	42 (95.5)	45 (93.8)	0.13 (<i>p</i> = 0.72)
Complete objective analgesia	41 (93.2)	41 (85.4)	1.43 (<i>p</i> = 0.23)
Complete subjective analgesia	35 (79.5)	36 (75.0)	0.27 (<i>p</i> = 0.60)

The only intra-operative complication which occurred was posterior capsule rupture, which occurred once in the hyaluronidase group and twice in the control group and was not felt by the surgeon to be attributable to poor anaesthesia in any case. The subjective impression of the surgeon was that the anaesthetic technique used produced consistently soft eyes following ocular compression in both groups of patients.

DISCUSSION

Hyaluronidase was found to confer no benefit on the efficacy of peribulbar anaesthesia in this prospective randomised study. With the technique used excellent globe akinesia, eyelid paralysis and analgesia were achieved in the majority of patients whether or not the enzyme was added.

Previous studies on the value of hyaluronidase in peribulbar anaesthesia have produced conflicting results with two reporting a benefit,^{4,5} one reporting benefit only in addition to specific combinations of other agents,⁶ one reporting benefit only if the anaesthetic solution was alkalised⁷ and one reporting no benefit.³ The discrepancy between these results may be attributable at least in part to a number of confounding variables. Many factors influence the effectiveness of a peribulbar block: injection technique; choice, concentration, volume and pH of anaesthetic agent; and anaesthetic interval.

Firstly, the injection site is important since it affects the speed of onset of the block and possibly its ultimate efficacy. Some surgeons inject the anaesthetic well away from the muscle cone near the bony walls of the orbit. In our experience this is a less reliable technique and we attempt to place the injection nearer to the muscle cone, whilst always remaining extra-conal. Such a technique was used in this study.

Secondly, the anaesthetic solution itself must be considered. The choice of anaesthetic agent probably has minimal influence, all the commonly used agents being effective at the concentrations used and differing mainly in their duration of action. The volume of anaesthetic solution may well affect the quality of a block; both studies reporting benefit from hyaluronidase used smaller volumes of injectate.^{4,5} One of these studies⁴ was not masked for the use of hyaluronidase, which may have introduced inadvertent bias to the results. The effect of anaesthetic solution pH on peribulbar block efficacy is unclear. Both local anaesthetic agents and hyaluronidase are more effective in alkaline solution. Two studies have found that alkalisation of the anaesthetic solution (to a pH of 6.7) improved the quality of peribulbar blocks containing hyaluronidase.^{7,8} It was proposed that hyaluronidase may have an additional protective effect against precipitation of anaesthetic agents in

alkaline solution. However, a third study found no such benefit⁹ and another study¹⁰ found no improvement of efficacy from addition of hyaluronidase to an alkalised solution of bupivacaine. Thirdly, the anaesthetic interval is an important parameter for the quality of a peribulbar block. A sufficient interval (generally at least 10 minutes) is required to allow the anaesthetic agents to diffuse to their site of action and also to allow intraorbital tension to return to normal following the injection. Both these processes may be facilitated by ocular compression. Hyaluronidase has been shown to accelerate the onset of anaesthesia in retrobulbar blocks¹¹ and may have a similar effect for peribulbar anaesthesia, though this has not been reported.

A much higher concentration of hyaluronidase (150 IU/ml) was used in this study than in previous studies, in which the concentration ranged from 7.5 IU/ml⁶ to 50 IU/ml.⁵ Despite this no benefit was found from its use. One study which found some benefit from using 7.5 IU/ml hyaluronidase obtained no additional benefit from doubling its concentration,⁶ suggesting that concentration of the enzyme is not important above a certain threshold. It is conceivable that such a high concentration of hyaluronidase might decrease the duration of the block by speeding diffusion of the anaesthetic away from the site of action, hence hiding a potential benefit from a smaller concentration of the agent. If this were the case, however, we might have expected to see a trend towards the hyaluronidase group having poorer intra-operative akinesia as compared with pre-operative akinesia, whereas in fact the opposite trend was found.

There are potential criticisms of this study. Sensitivity in detecting an effect of hyaluronidase might have been reduced by stratification of the data from the visual analogue scores. Even when the data were not stratified, however, and the Mann-Whitney *U*-test (adjusted for ties) was used to compare scores, no statistically significant difference between the two groups was found for any category. The study was also limited in its power to detect a small benefit from hyaluronidase. The sample sizes used were sufficient to detect a difference in effect of about 20% (at 80% power), but to have detected a difference of only 5% at that power would have required sample sizes of nearly 1000 patients in each group. Against the possibility that the study hides a small benefit from the enzyme, however, was the finding that the greatest difference between the two groups demonstrated a better result in the control group. The proportion of patients with complete pre-operative akinesia was higher in the control group (72.9%) than in the hyaluronidase group (59.1%), though this did not reach statistical significance.

Does hyaluronidase have any role to play in peribulbar anaesthesia? It is our experience that poor anaesthesia usually results from poor technique or too short an anaesthetic interval. In these situations hyaluronidase might be of some benefit and therefore may be of use when trainees are learning the technique. However, the use of hyaluronidase carries a low but finite risk of potentially serious allergic reaction.¹² In addition, destruction of the orbital interstitial tissue barriers may have some long-term effects. Finally hyaluronidase is not cheap, costing £4 per ampoule (1500 IU) at current NHS prices.

In conclusion, this study demonstrates that no significant benefit is obtained from the routine use of hyaluronidase in peribulbar anaesthetic techniques using standard anaesthetic agents and adrenaline. It is possible to achieve consistently excellent results without it.

Key words: Hyaluronidase, Peribulbar, Anaesthesia, Akinesia.

REFERENCES

1. Davis DB II, Mandel MR. Efficacy and complication rates of 16 224 consecutive peribulbar blocks: a prospective multicentre study. *J Cataract Refract Surg* 1994;20:327–37.
2. Bloomberg LB. Administration of periocular anesthesia. *J Cataract Surg* 1986;12:677–9.
3. Crawford M, Kerr WJ. The effect of hyaluronidase on peribulbar block. *Anaesthesia* 1994;49:907–8.
4. Morsman CD, Holden R. The effects of adrenaline, hyaluronidase and age on peribulbar anaesthesia. *Eye* 1992;6:290–2.
5. Sarvela J, Nikki P. Hyaluronidase improves regional ophthalmic anesthesia with etidocaine. *Can J Anaesth* 1992;39:920–4.
6. House PH, Hollands RH, Schulzer M. Choice of anesthetic agents for peribulbar anesthesia. *J Cataract Refract Surg* 1991;17:80–3.
7. Roberts JE, MacLeod BA, Hollands RH. Improved peribulbar anesthesia with alkalinisation and hyaluronidase. *Can J Anaesth* 1993;40:835–8.
8. Zahl K, Jordan A, McGroarty J, Gotta AW. pH-adjusted bupivacaine and hyaluronidase for peribulbar block. *Anesthesiology* 1990;72:230–2.
9. Lewis P, Hamilton RC, Brant R, Loken RG, Maltby JR, Strunin L. Comparison of plain with pH-adjusted bupivacaine with hyaluronidase for peribulbar block. *Can J Anaesth* 1992;39:555–8.
10. Mather C, Hayden Smith J, Bloom PA. The efficacy of 0.75% bupivacaine with pH adjustment and hyaluronidase for peribulbar blockade: the incidence of prolonged ptosis. *Eur J Ophthalmol* 1994;4:13–8.
11. Wood G, Simpson T. The effect of hyaluronidase on the onset of retrobulbar anaesthesia. *Can J Anaesth* 1990;37:562.
12. Compendium of Pharmaceuticals and Specialties. Ottawa: Canadian Pharmaceutical Association, 1990: 1193.