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The use of hyaluronidase in nasal infiltration: prospective randomized controlled pilot study

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Abstract

A double-blind randomized prospective case-control pilot study was performed to assess tissue distortion caused by the infiltration of local anaesthetic to the dorsum of the nose and to see if this was altered by the addition of hyaluronidase. Forty patients undergoing nasal manipulation for fractured nasal bones were randomized to receive either 4 ml of two per cent lignocaine and adrenaline 1:200 000 or 4 ml of two per cent lignocaine and adrenaline 1:200 000 with 1500 IU hyaluronidase, which was infiltrated subcutaneously over the nasal dorsum. One surgeon using a standardized technique performed the nasal infiltration. Other outcome measures were ease of manipulation, adequacy of the reduction, patient satisfaction with cosmesis and patient analgesia requirements. There were trends for decreased tissue distortion and improved ease of manipulation in the hyaluronidase group. Larger trials are required to confirm these results.

Key words: Nasal Bone; Fractures; Hyaluronoglucosamindase; Treatment Outcome

Introduction

Hyaluronidase is an enzyme that decreases the viscosity of the ground substance, or tissue cement of cells, by reversibly binding to hyaluronic acid. It is used in many areas of surgery including gynaecology, ophthalmology, plastic and general surgery as well as in radiology, oncology, and palliative medicine.[1] In all these areas the ability of hyaluronidase to aid in the resorption of excess fluid or blood in subcutaneous or intramuscular compartments is utilized. Hyaluronidase does this by allowing fluids to move more easily along tissue planes thereby increasing its area of distribution.[1] In surgery hyaluronidase is used primarily in conjunction with local anaesthetics. It is used here to decrease tissue distortion caused by the local anaesthetic and to increase the area that the anaesthetic infiltrates. There are limited reports of the use of hyaluronidase in nasal surgery. This study assesses the effectiveness of hyaluronidase in decreasing the tissue distortion caused by a local anaesthetic solution injected subcutaneously over the nasal dorsum.

Method

Forty patients were to be enrolled in the trial. Ethical approval was obtained from the Ayrshire and Arran Local Research Ethics Committee. Inclusion criteria were that the patients were able to give informed consent, were 16 years of age or older and had displaced nasal fractures, which had occurred no more than 21 days prior to the date of manipulation. Exclusion criteria are listed in Table I.

Patients were initially seen five to seven days post-trauma in a clinic and were offered enrolment into the trial. They received at this time both a verbal description of the trial as well as a written information sheet. If they agreed to participate they were advised to use paracetamol-based analgesia in preference to non-steroid anti-inflammatory drug (NSAID)s until surgery. Informed consent was obtained prior to surgery. Randomization was performed prior to induction of the general anaesthesia, by an anaesthetic technician using a random number generator. The anaesthetic technician then prepared either 4 ml of two per cent lignocaine with adrenaline or the same solution with 1500 IU of hyaluronidase anhydrous powder made up to 4 ml. An independent observer assessed the nose immediately prior to infiltration of the local anaesthetic then left the room. All independent observers were either trained otolaryngologists or otolaryngology trainees. Local anaesthetic was injected subcutaneously from a single point at the root of the nose, by infiltrating inferiorly and laterally on each side of the nasal dorsum using a standardized technique. Infiltration was performed by a single injector, (SHV), for all patients. The injector then massaged the

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TABLE I
EXCLUSION CRITERIA

- any evidence of infection in the area of nasal trauma
- any coexisting malignancy
- pregnancy or lactation
- previous allergy to hyaluronidase
- previous or active rheumatic fever
- using any of the following medications concomitantly; NSAIDs, heparin, aminoglycosides, vitamic C or antihistamines.

dorsum of the nose for two minutes. The independent observer then returned and independently graded the distortion of the nose by the infiltrate on a scale of 0–3 (0 = no distortion, 1 = minimal distortion, 2 = moderate distortion, 3 = marked distortion). The injector also assessed the tissue distortion using the same scale. The injector and the observers were all blinded to the group allocation and to each other. When a difference occurred between the independent observers' tissue distortion score and the injector's, the score of the independent observer was used as the definitive score for statistical analysis. The nasal fracture was then manipulated either manually or with Walsham's forceps by the injector/surgeon (SHV). Ease of manipulation was assessed by the surgeon on a scale of 1–5 (1 = very easy, 2 = easy, 3 = minimal difficulty, 4 = moderate difficulty, 5 = very difficult). The surgeon then assessed the result of the manipulation as either complete or incomplete. A pain score was recorded 30 minutes post-operatively using a visual analogue scale (0–10 cm). Requirement for additional analgesia was noted and it was later noted if further analgesia was required before discharge. Patient satisfaction with cosmesis was reviewed immediately prior to discharge on a score of 1–3 (1 = satisfied, 2 = unsure, 3 = dissatisfied). All complications were noted.

Patients were contacted by telephone at one to four weeks to again assess patient satisfaction and were also asked if there had been any complications.

Results

Between 01/01/2001 and 31/01/2002, 40 patients undergoing manipulation of fractured nasal bones under general anaesthetic were recruited. Twenty received local anaesthetic with hyaluronidase and 20 without. The male to female ratios were 16:4 in the hyaluronidase group and 17:3 in the non-hyaluronidase group. The median age of the hyaluronidase group was 22.5 years (range 16–53 years) and the median age of the non-hyaluronidase group was 20 years (range 16–59 years). The mean number of days since fracture was 12.4 days in the hyaluronidase group (range 8–16 days) and 11.8 days in the non-hyaluronidase group (range 7–16 days). Four (20 per cent) of the 20 patients in the hyaluronidase group had had previous nasal fractures whereas five (25 per cent) of the non-hyaluronidase group had had previous nasal fractures. The distribution of fracture types was similar in the two groups. The hyaluronidase group had 14 lateral (70 per cent), two depressed (10 per cent), one impacted (five per cent) and three (15 per cent) mixed type fractures. The non-hyaluronidase group had 14 lateral (70 per cent), two depressed (10 per cent), two impacted (10 per cent) and two (10 per cent) mixed type fractures.

Distortion assessment by the independent observers following injection of local anaesthetic in the hyaluronidase group showed that two (10 per cent) had no distortion and 18 (90 per cent) had mild distortion. In the non-hyaluronidase group one (five per cent) had no distortion, 16 (80 per cent) had mild distortion and three (15 per cent) had moderate distortion (Figure 1). There was a 90 per cent concordance between the independent and the second (injectors) observers' assessment of tissue distortion caused by the infiltration of local anaesthetic. There was a trend for the hyaluronidase group to have less distortion but this was not statistically significant ($p = 0.107$; Wilcoxon test). Surgeon satisfaction with the initial outcome of the manipulation was 17/20 (85 per cent) in the hyaluronidase group and 16/20 (80 per cent) in the non-hyaluronidase group. Assessment of ease of manipulation showed a trend for easier manipulation in the hyaluronidase than the non-hyaluronidase group (Figure 2), however, there was no statistical difference between the two groups ($p = 0.089$; Wilcoxon test). Patient satisfaction was 18/20 (90 per cent) on the day of surgery and 20/20 (100 per cent) at one to four weeks for the hyaluronidase group and 15/20 (75 per cent) on the day of surgery and 18/20 (90 per cent) at one to four weeks for the non-hyaluronidase group. One (five per cent) of the hyaluronidase group required pain relief at 30 minutes whereas three (15 per cent) of the non-hyaluronidase group did. The average visual analogue pain score at 30 minutes was 0.3 cm for the hyaluronidase group and 0.9 cm for the non-hyaluronidase group. At the time of discharge none of the hyaluronidase group and one (five per cent) of the non-hyaluronidase group required pain relief. No adverse reactions occurred in either group. Calcula-

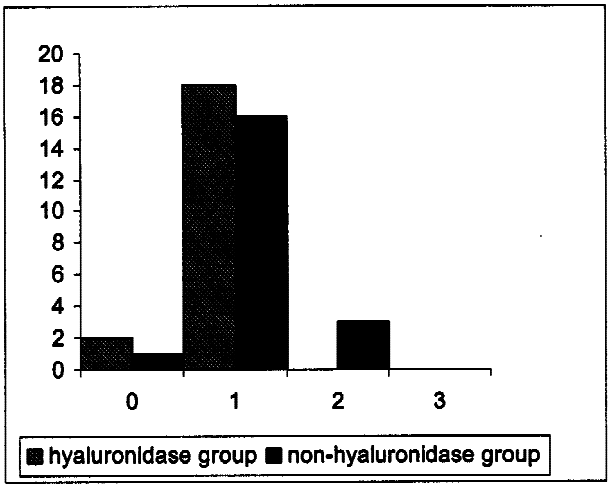

FIG. 1

Tissue distortion after the injection of 2 per cent lignocaine with adrenaline both with and without hyaluronidase. (0 = no distortion; 1 = mild distortion; 2 = moderate distortion; 3 = severe distortion).

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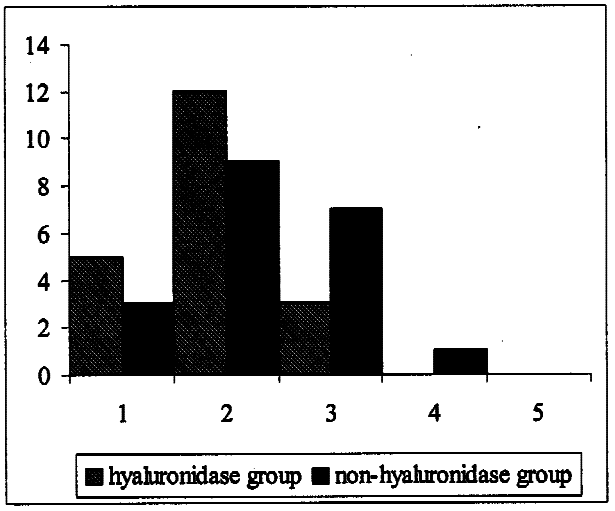

FIG. 2

Ease of manipulation of fractured nasal bones after the injection of 2 per cent lignocaine with adrenaline both with, and without, hyaluronidase. (1 = very easy; 2 = easy; 3 = minimal difficulty; 4 = moderate difficulty; 5 = very difficult).

tions of effect size for tissue distortion (0.595) and ease of manipulation (0.574) determined that for these parameters to be proven statistically different, trials with 46 patients and 50 patients in each arm respectively, would be required.

Discussion

The aim of this study was to identify whether or not the addition of hyaluronidase to lignocaine with adrenaline facilitated the spread of the injected anaesthetic to a degree that a difference in tissue distortion was discernible clinically. Hyaluronidase is an enzyme, which has a specific action on the mucopolysaccharide hyaluronic acid. Hyaluronic acid is a component of the mucoprotein ground substance or tissue cement of the tissue spaces. Hyaluronidase reversibly depolymerizes hyaluronic acid and thereby reduces the viscosity of the tissue cement and facilitates the diffusion of injected substances within the tissue planes. Therapeutically this effect can be used to increase the absorption of subcutaneously or intramuscularly injected fluids as well as to promote the absorption of excess fluids and extravasated blood in the tissues.[1–4] The principal drawback of using local anaesthetics in nasal procedures is the associated tissue distortion. Lewis-Smith[5] and Nevarre and Tzarnas[6] in their respective papers noted the minimal loss of surface contour due to the rapid spread of subcutaneous infiltrate when hyaluronidase was added to a solution of local anaesthetic. This occurred both with,[5] and without,[6] adrenaline.

A Medline search into the use of hyaluronidase in nasal surgery identified a single study. Fry[7] in 1967 described the manipulation of fractured nasal bones and septums using a subcutaneous infiltration over the nasal dorsum with lignocaine, adrenaline and hyaluronidase, and intranasal packing impregnated with cocaine and adrenaline. This was performed both with, and without, general anaesthesia. No attempt was made to assess tissue distortion. Because of the lack of evidence based medicine to support the use of hyaluronidase in this area we elected to perform a pilot study. The study size of 40 patients was chosen having obtained statistical advice.

In this study we have demonstrated a trend for the hyaluronidase group to have less tissue distortion than the non-hyaluronidase group, which is consistent with the existing research in this area. We also demonstrated a trend in the hyaluronidase group for easier manipulation. This may be a perceived effect with less tissue distortion and resorption of local oedema[7] and bruising[8] making the manipulation easier. It could also be due to the hyaluronidase binding to hyaluronic acid in the callus and destabilizing the fracture line. If this were true it would be expected that the hyaluronidase group would have more late displacements. This, however, did not appear to occur as patient satisfaction with cosmesis at one to four weeks was greater in the hyaluronidase group (100 per cent) than the non-hyaluronidase group (90 per cent). The cause of this trend remains uncertain.

The calculation of effect sizes for tissue distortion (0.595) and ease of manipulation (0.574) are significant if this pilot demonstrates a true trend. Using these effect sizes it can be calculated that it would require total group sizes of 96 and 100 patients to confirm these respective trends statistically. Although the differences in tissue distortion measured are on quite a gross scale, to be able to demonstrate these changes with such small numbers would infer clinical significance. This can also be implied for the trend of ease of manipulation.

The main theoretical disadvantages of the use of hyaluronidase in conjunction with local anaesthetics are a decreased duration of action of the anaesthetic, increased peak plasma concentrations of the anaesthetic and the risk of anaphylactic reactions to hyaluronidase. Several authors[5,9,10] have demonstrated that hyaluronidase decreases the duration of local anaesthetics both with and without, adrenaline. Lewis-Smith[5] however has also demonstrated that 10 ml of one per cent of lignocaine with 1:200 000 adrenaline and 1500 IU of hyaluronidase injected subcutaneously to the volar aspect of the forearm gives effective anaesthesia in human subjects for at least four and a half hours. We were unable to demonstrate any increase in pain relief requirements in the hyaluronidase group. In fact, the hyaluronidase group required less analgesia both 30 minutes post-operatively (five per cent *vs* 15 per cent) and at discharge (0 per cent *vs* five per cent). The safety of hyaluronidase has been well demonstrated clinically in an audit of 6000 local anaesthetic peribulbar blocks by Nicholl *et al.*[11] We did not experience any adverse reactions in either group.

There are various drugs that are used in clinical practice that inhibit the action of hyaluronidase. These include heparin, aminoglycosides, salicylates, antihistamines and vitamin C.[2,3] The concomitant uses of these medications were therefore exclusion criteria. We advised patients when they initially

attended clinic that they should use paracetamol-based analgesia instead of NSAIDs. A previous medical history of rheumatic fever was also an exclusion criterion as there have been reports of antibodies to hyaluronidase in these patients.[2]

- **Previous studies have suggested that an infiltration of hyaluronidase, with or without adrenaline, reduces tissue distortion prior to manipulation of a fractured nose**
- **This prospective randomized trial compared locally infiltrated hyaluronidase and local anaesthetic in aiding manipulation of the nose**
- **The trial was blinded and outcome measurements assessed were tissue distortion, ease of manipulation, adequacy of reduction, patient satisfaction and requirement for post-operative analgesia**
- **The hyaluronidase group demonstrated a tendency to reduced tissue distortion and improved ease of manipulation but these findings were not significant statistically**
- **A calculation of effect size shows that the power of the study would need to be increased if significance for these parameters is to be confirmed**

The technique of nasal injection used was a modification of a technique described by both Waldron *et al.*[12] and Watson *et al.*[13] They described, in their respective papers, a single injection point at the root of the nose, giving a regional block of both infratrochlear and external nasal nerves. The volume of local anaesthetic used when reducing fractured noses under local anaesthesia varies between authors with volumes of between 2–4 ml being reported.[12–16] We elected to use 4 ml as we felt that this volume would enable more effective anaesthesia of the branches of the intra-orbital nerves to the nose.

Cosmetically a satisfactory result was achieved in 95 per cent of our patients as judged by the patients (100 per cent hyaluronidase *vs* non-hyaluronidase) and 82.5 per cent as judged by the surgeons (85 per cent hyaluronidase *vs* non-hyaluronidase). These results compare favourably with those of Murray and Maran,[16] Owen *et al.*[17] and Dickson and Sharpe[18] who showed patient satisfaction with cosmesis following nasal manipulation to be between 70–83 per cent. Owen *et al.*[17] also assessed surgeon satisfaction at the time of surgery and found that 71 per cent of fractures were completely reduced at the time of surgery. Patient and surgeon satisfaction will diminish with time as some fractures inevitably displace.

We acknowledge that there are some weaknesses in this trial. Several independent observers were used to determine tissue distortion. However, to enhance the quality of the measurement of tissue distortion the injector acted as a second observer throughout the trial. This demonstrated a 90 per cent agreement between the independent observers' and the second observer's (injector) assessment of tissue distortion. The injector was blinded to group allocation but may have been able to identify which patients received hyaluronidase purely on palpation by ease of fluid resorption. This could have introduced bias. To eliminate this potential bias, only the result of the independent observer was used for statistical analysis to assess tissue distortion. We also acknowledge that longer follow-up times may have altered patient satisfaction rates.

In conclusion, we were unable to demonstrate any statistically significant differences between the hyaluronidase and non-hyaluronidase groups in any of the parameters measured. In the areas of tissue distortion and ease of manipulation there were trends in favour of the hyaluronidase group. There may be a difference using hyaluronidase with these two parameters, which we were unable to demonstrate because of our small trial size and the grading scale used. This may prove important especially in the areas of rhinoplasty and manipulation of fractured nasal bones solely under local anaesthetic, where small changes in tissue distortion can mask cosmetic deformities. Further research in this area with larger trials is required to confirm these apparent trends.

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References

1 Watson D. Hyaluronidase. *Br J Anaesth* 1993;**71**:422–5
2 Dollery CT, ed. *Therapeutic Drugs*. Edinburgh, London: Churchill Livingstone, 1991;**1**:H41–4
3 Menzel EJ, Farr C. Hyaluronidase and its substrate hyaluronan: biochemistry, biological activities and therapeutic uses. *Cancer Letters* 1998;**131**:3–11
4 Reynolds JEF, ed. *Martindale: the Extrapharmacopoeia 31st Edition*. London: Royal Pharmaceutical Society, 1996;1714.1
5 Lewis-Smith PA. Adjunctive use of hyaluronidase in local anaesthesia. *Br J Plast Surg* 1986;**39**:554–8
6 Nevarre DR, Tzarnas CD. The effects of hyaluronidase on the efficacy and the pain of administration of 1% lidocaine. *Plast Reconstruct Surg* 1998;**101**:365–9
7 Fry H. The importance of the septal cartilage in nasal trauma. *Br J Plast Surg* 1967;**20**:392–402
8 Chaung VP. Hyaluronidase for the treatment of hematoma at an angiographic puncture site. *Radiology* 1983;**146**:227
9 Pettersson LO, Akerman B. Influence of hyaluronidase upon local infiltration anaesthesia by lidocaine. *Scand J Plast Reconstruct Surg* 1984;**18**:297–301
10 Keeler JF, Simpson KH, Ellis FR, Kay SP. Effect of addition of hyaluronidase to bupivicaine during axillary brachial plexus block. *Br J Anaesth* 1992;**68**:68–71
11 Nicoll JMV, Arun PA, Ahlen K, Baguneid S, Edge RE. Central nervous system complications after 6000 retrobulbar blocks. *Anesth Analg* 1987;**66**:1298–302
12 Waldron J, Mitchell DB, Ford G. Reduction of fractured nasal bones; local versus general anaesthesia. *Clin Otolaryngol Allied Sci* 1989;**14**:357–9
13 Watson DJ, Parker AJ, Slack WT, Griffiths MV. Local versus general anaesthetic in the management of the fractured nose. *Clin Otolaryngol Allied Sci* 1998;**13**:491–4

14 Cook JA, McRae DR, Irving RM, Dowie LN. A randomized comparison of manipulation of the fractured nose under local and general anaesthesia. *Clin Otolaryngol Allied Sci* 1989;**15**:343–6

15 Cook JA, Murrant NJ, Evans KL, Lavelle RJ. Manipulation of the fractured nose under local anaesthesia. *Clin Otolaryngol Allied Sci* 1992;**17**:337–40

16 Murray JAM, Maran AGD. The treatment of nasal injuries by manipulation. *J Laryngol Otol* 1980;**94**:1405–10

17 Owen GO, Parker AJ, Watson DJ. Fractured nose reduction under local anaesthesia. Is it acceptable to the patient? *Rhinology* 1992;**30**:89–96

18 Dickson MG, Sharpe DT. A prospective study of nasal fractures. *J Laryngol Otol* 1986;**100**:543–51

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