

Hyaluronidase revisited: A comparison of axillary plexus block with and without recombinant human hyaluronidase

Annelot C Krediet¹, Nizar Moayeri², Gerbrand J Groen³, Aaron Hess⁴ and Paul E Bigeleisen^{5*}

¹Department of Anesthesiology University Medical Center Utrecht, USA

²Department of Neurosurgery University Medical Center Utrecht, USA

³Department of Anesthesiology, Pain Center, University Medical Center Groningen, USA

⁴Department of Anesthesiology, University of Baltimore at Maryland, USA

Abstract

Study objectives: To study whether a human recombinant formulation of hyaluronidase (rHuPH20, available as Hylenex®, Baxter Corp.) facilitates local anesthetic spread in axillary plexus blocks.

Design: Randomized controlled trial.

Setting: The pre-operative care area of an ambulatory surgery center.

Patients: 59 adult patients, ASA status I–IV, undergoing surgery of the elbow, forearm or hand.

Interventions: Patients were allocated to receive a single-injection axillary brachial plexus block with (n=31) or without (n=28) the addition of 150 Units rHuPH20 (volume=1 ml, cost=\$150.00) to a local anesthetic solution of bupivacaine 2.5 mg/ml, lidocaine 10 mg/ml and epinephrine 3 mcg/ml.

Measurements: A composite score of sensory and motor examination at 20 minutes post-injection (0–16 points). Block success was defined as a minimal composite score of 14 points.

Main results: Overall success rate was 39% in the control group and 29% in the treatment group. The mean composite score per patient was 11.9 (95%CI: 10.7–13.0) in the control group and 11.7 (95%CI: 11.0–12.4) in the treatment group. None of these differences were statistically significant.

Conclusions: Block success rates for single-injection axillary plexus block were unaffected by the addition of 150U rHuPH20.

Introduction

Hyaluronidase degrades hyaluronic acid, promoting the flow of drugs through tissue [1]. It has been available as an additive to local anesthetic solutions since 1948. Its most common anesthesia application is in ophthalmic cases. For upper and lower extremity nerve blocks, its usage has been abandoned since little beneficial effects on block success, speed of onset, or duration of block were found [2–6]. However, there are a number of reasons to reassess its use. First, few of these studies meet quality standards concerning the random allocation of treatment and a control group or blinded assessment of outcomes. In addition, sample sizes were small. Moreover, ultrasound guidance may increase the effectiveness of hyaluronidase as it allows for precise targeting of the injection close to the nerve(s). Most importantly, previous studies have tested animal-derived hyaluronidases which contain impurities which may influence the intended effect of the active ingredient [7]. In 2005, a human recombinant formulation (rHuPH20, available as Hylenex, Baxter Corp., Dearfield, IL) was approved by the FDA which has approximately 100-times greater purity (measured by specific activity) than the bovine testes-derived hyaluronidases [1]. Thus, rHuPH20 may be more effective in facilitating local anesthetic spread than the animal-derived preparations.

This point may be particularly relevant for axillary plexus block, since incomplete blocks are generally attributed to limited spread

of local anesthetic fluid due to connective tissue barriers within the auxiliary sheath [8–13]. Many practitioners elect to perform multiple injections to ensure each nerve is adequately covered. As multiple injections are associated with more needle passes and a longer procedural time, a single injection technique is desirable provided that it is equally effective [14].

In order to re-evaluate hyaluronidase usage for peripheral nerve blockade, a double-blinded clinical study was performed in patients receiving an axillary brachial plexus block with or without rHuPH20 added to a local anesthetic solution of bupivacaine 2.5 mg/ml, lidocaine 10 mg/ml and epinephrine 3 mcg/ml. Block success at 20 min constituted the primary outcome of the study.

Materials and methods

The study protocol was approved by the Institutional Review

Correspondence to: Paul Bigeleisen, Department of Anesthesiology, University of Baltimore at Maryland, 22 South Greene Street, Baltimore MD 21201, USA, Tel: 301-938-9069; E-mail: Pbigeleisen@anes.umm.edu

Key words: anesthesia, local, nerve block, hyaluronic acid, axilla

Received: May 10, 2015; **Accepted:** June 03, 2015; **Published:** June 07, 2015

Board of Lindsay House Surgery Center, Penfield, NY. All patients gave written informed consent to take part in the study. A total of 64 patients, ASA status I–IV, who agreed to an axillary brachial plexus block for surgery of the elbow, forearm or hand were enrolled in the study. Patients with known neurological dysfunction were excluded from the study. Patients were allocated to treatment or control group based on the last digit of their medical record number. Nerve block in the control group was performed with a mixture of bupivacaine 2.5 mg/ml, lidocaine 10 mg/ml and epinephrine 3 mcg/ml (29 ml) and 1 ml of normal saline. 150 units of rHuPH20 (volume=1 ml) (Hylenex®, Baxter Corp., Deerfield, IL) was added to 29 ml of the same anesthetic mixture in the treatment group. 150 units of Hylenex is the default dose recommended by the manufacturer to increase dispersion and absorption of injected drugs. All solutions were prepared by a nurse prior to the procedure and the physician performing the procedure was blinded to the contents of the local anesthetic solution.

Routine monitors were applied and each patient was sedated with fentanyl (50–100 mcg) and midazolam (1–2 mg). After aseptic preparation, the axilla was imaged with a 12 MHz, 38 mm linear probe (Terason, Boston, MA). A 22 gauge stimulating needle was used for all blocks (B-Braun, Bethlehem, PA). All injections were targeted at the radial nerve to standardize the location of injection for all study participants. Also, radial-nerve stimulation has been found to produce more extensive anesthesia than median-nerve stimulation or ulnar-nerve stimulation [15–16]. Once the radial nerve was identified on ultrasound deep to the axillary artery, this location was confirmed with electrostimulation (B-Braun, Bethlehem, PA) by extension of the elbow or wrist using a stimulation frequency of 2 Hz, a pulse width of 0.1 m sec and current of 1.5 mA. Subsequently, a total of 30 ml of local anesthetic mixture (control group) or local anesthetic/ Hylenex mixture (study group) was injected around the radial nerve. Patients were excluded if identification of radial nerve with electrostimulation did not elicit an extension of the elbow or wrist joint.

Block assessment was performed 20 minutes after injection by the same anesthesiologist who performed the injection. Sensory block was evaluated by the pinprick method in the nerve distribution of the radial nerve (dorsum of thumb), ulnar nerve (palmar aspect of fifth finger), median nerve (palm of the hand) and musculocutaneous nerve (lateral aspect of forearm). A three-point scoring system was used: 0=normal sensation; 1=impaired sensation; 2=loss of sensation. Motor block was assessed in the nerve distribution of the radial nerve (wrist extension), ulnar nerve (adduction of fourth and fifth finger), median nerve (flexion of the distal phalangeal joint on the second finger) and musculocutaneous nerve (flexion of the elbow), with the following scoring: 0=normal motor function; 1=impaired motor function; 2=no motor function. All scores were added to calculate a composite score between 0 (no block) and 16 (full motor and sensory block). “Block success” was defined as a minimal composite score of 14 points, provided the sensory block score was equal or greater than 7 [17–18].

Statistical analysis

The sample size calculation was based on the primary outcome, block success. Based on previous studies using single-injection auxiliary plexus block a 60% success rate [19–23] was expected. Assuming that the addition of Hylenex would increase block success to 90%, the sample size was calculated at 29 patients per group for $\alpha=0.05$ and a power of 80%. Using a multiple injection technique, success rates $\geq 90\%$ have repeatedly been found to be feasible. Fisher’s exact test and Student’s t-test were used for categorical and continuous data respectively [24].

All calculations were done using Microsoft Excel and GraphPad Quick Calcs (La Jolla, USA). Comparisons of baseline demographics were performed using Student’s t-test or Person’s chi squared test as applicable.

Results

In four patients, (1 patient in the treatment group, 3 patients in the control group) no motor response could be elicited with electrostimulation after identification of the radial nerve on ultrasound. In one patient, an inadvertent intraneural injection in the radial nerve occurred (treatment group). These patients were excluded from the study. A total of 31 patients in the treatment group and 28 patients in the control group completed the study. Baseline characteristics are shown in Table 1. The control group was found to have a higher weight ($p=0.023$) and BMI ($p=0.033$). The age of control and study groups were not different ($p=0.557$). There was no difference in ASA status ($p=0.285$) between groups or male sex ($p=0.728$).

Overall success rate was 39% in the control group and 29% in the treatment group. The mean composite score per patient was 12.1 (95%CI: 11.0–13.2) in the control group and 12.3 (95%CI: 11.6–13.0) in the treatment group. None of these differences were statistically significant (Table 2). No adverse reactions to the local anesthetic solution were observed with or without rHuPH20.

Discussion

In this study, 59 patients underwent single-injection axillary brachial plexus block targeted at the radial nerve with ultrasound and electro-stimulation. The addition of 150U of rHuPH20 to a local anesthetic solution of 29 ml containing bupivacaine 2.5 mg/ml, lidocaine 10 mg/ml and epinephrine 3 mcg/ml had no effect on motor and sensory blockade at 20 min.

This is the largest clinical trial so far on the usage of hyaluronidase in peripheral nerve blocks and the first one using rHuPH20 for this indication. These results correspond to that of previous studies which found no apparent benefit from the addition of animal-derived hyaluronidase to the local anesthetic solution in peripheral nerve blocks [2–6].

Limitations

The aim of this study was to explore any potential benefits of

Table 1. Baseline characteristics.

	n	Age in years	Sex, male	Height in cm	Weight in kg	BMI
Control	28	49 (17)	13 (46%)	172 (11)	93 (23)	32 (8)
rHuPH20	31	52 (17)	12 (39%)	169 (10)	81 (17)	28 (5)
P value		0.557	0.728	0.643	0.023	0.033

Data are presented as means (SD) or numbers (%)

Table 2. Block success at 20 minutes.

Outcome	Control	rHuPH20	Test statistic
Successful block (composite score ≥ 14)	39% \pm 18%	29% \pm 16%	P = 0.29
Complete radial nerve block	89% \pm 11%	90% \pm 10%	P = 1.00
Complete ulnar nerve block	68% \pm 17%	84% \pm 13%	P = 0.22
Complete median nerve block	43% \pm 18%	55% \pm 18%	P = 0.44
Complete musculocutaneous nerve block	14% \pm 13%	10% \pm 10%	P = 1.00
Mean composite score	12.1 \pm 1.1	12.3 \pm 0.7	P = 0.82

Data are presented as proportions or means \pm 95% confidence interval

rHuPH20 for single-injection axillary plexus blockade. Taking into account previous negative results, the study had to pose minimal burden on participating patients and the medical center. This is reflected in the study design. Most importantly, motor and sensory assessment was performed at 20 min only, and blocks subsequently supplemented if necessary for the surgical procedure. In particular, a separate injection for the musculocutaneous nerve could be performed immediately before the surgery. In routine clinical care, the patients in this study would have received a double or triple-injection axillary plexus block. For the study, we scheduled a 20 min time interval between the first and any subsequent injections (if indicated). This is the standard protocol at our institution for all patients who receive upper extremity blocks and was mandated by the surgeons. It is likely that blocks would have progressed given more time. However, additional physical exams and/or delaying supplementation were not feasible given the busy operating schedule. The relatively brief time period for block onset is likely the cause that the success rates reported in this study are lower than in previous studies.

Patients were allotted to treatment and control based on the last digit of their medical record. This method was chosen as it was more time-efficient and practical for nursing staff preparing the local anesthetic solutions. The medical record number was unknown to the anesthesiologist during block performance and the motor/sensory examination. Medical record numbers were assigned sequentially to patients at the time of admission. The study was conducted over a period of two months during which a total of 759 patients were admitted and who had surgeries of all types. Imbedded within these medical record numbers were the 64 patients who were allocated to the study and control groups.

A relatively small sample size was chosen which meant the study lacked power to detect differences <30% for the primary outcome i.e. proportion of patients with composite score ≥ 14 . However, it should be considered that the mean composite scores in control and treatment group are practically identical (12.1 and 12.3 points, respectively). For this continuous outcome, the study had adequate power to detect a difference of >2 points. It seems therefore unlikely that a larger sample size would have led to a different conclusion. The control group had a higher mean weight and BMI. We do not believe that the difference in weight or BMI contributed to the observed outcomes.

Conclusion

In this study, the addition of rHuPH20 to local anesthetics had no measurable effect on motor or sensory block of single-injection

axillary brachial plexus block. However, there may be advantages of this product that we failed to notice such as longer block duration or smaller amount of local anesthetic needed.

Disclosure

All authors have no financial or personal interest with other people or organizations that could inappropriately have influenced this work.

Financial sources

This work was funded by departmental sources of the department of anesthesiology at Linden Oaks Surgery Center, Rochester, NY. Baxter Corporation (Deerfield, IL) provided Hylenex for the study.

References

1. Rosenberg H, Sambuughin N, Riaz S, Dirksen R (2013) Malignant Hyperthermia Susceptibility. *Gene Reviews* 2013; Pagon RA, Adam MP, Ardinger HH, et al., editors. Seattle (WA): University of Washington, Seattle; 1993-2014.
2. Brandom BW, Bina S, Wong CA, Wallace T, Visoiu M, et al. (2013) Ryanodine receptor type 1 gene variants in the malignant hyperthermia-susceptible population of the United States. *Anesth Analg* 116: 1078-1086. [[Crossref](#)]
3. Sambuughin N, Holley H, Muldoon S, Brandom BW, de Bantel AM, et al. (2005) Screening of the entire ryanodine receptor type 1 coding region for sequence variants associated with malignant hyperthermia susceptibility in the north american population. *Anesthesiology* 102: 515-521. [[Crossref](#)]
4. Exome Variant Server. NHLBI Exome Sequencing Project. Seattle, WA, URL: <http://evs.gs.washington.edu/EVS/>. Accessed Feb 12, 2014.
5. Sambuughin N, Liu X, Bijarnia S, Wallace T, Verma IC, et al. (2013) Exome sequencing reveals SCO2 mutations in a family presented with fatal infantile hyperthermia. *J Hum Genet* 58: 226-228. [[Crossref](#)]
6. Hopkins PM (2011) Malignant hyperthermia: pharmacology of triggering. *Br J Anaesth* 107: 48-56. [[Crossref](#)]
7. Girard T, Treves S, Voronkov E, Siegemund M, Urwyler A (2004) Molecular genetic testing for malignant hyperthermia susceptibility. *Anesthesiology* 100: 1076-1080. [[Crossref](#)]
8. Litman RS, Rosenberg H (2005) Malignant hyperthermia: update on susceptibility testing. *JAMA* 293: 2918-2924. [[Crossref](#)]
9. Sei Y, Sambuughin N, Muldoon S (2004) Malignant hyperthermia genetic testing in North America Working Group Meeting. Bethesda, Maryland. September 4-5, 2002. *Anesthesiology* 100: 464-465. [[Crossref](#)]
10. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, et al. (1994) A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 80: 771-779. [[Crossref](#)]
11. Larach MG, Brandom BW, Allen GC, Gronert GA (2007) Failure to rescue from fulminant malignant hyperthermia: Deaths and their genetic variants. A 2052 ASA Annual Meeting 2013.