

A Review on Hyaluronidase as an Ideal adjuvant to Nerve Blocks.

Neeta Santha*

Associate Professor, Department of Anaesthesiology, Kasturba Medical college, Mangalore
Manipal Academy of Higher Education, Manipal, India
E mail -drneetas@yahoo.com

Abstract

Hyaluronidase has been used for decades as an adjunct to various drugs in medical field. Addition of the drug to local anaesthetic agent helps to improve the quality of anaesthesia. In this review article we are discussing about injectable hyaluronidase and its off label uses.

Introduction

Hyaluronidase is an enzyme that breaks down hyaluronic acid and increases absorption of other drug into tissues.¹ Hyaluronidase hydrolyses hyaluronic acid by splitting the glucosaminidic bond between C1 of the glucosamine moiety and C4 of glucuronic acid. This decreases the viscosity of the tissues and increases diffusion of injected fluids thus enhancing their absorption.²

Hyaluronic acid is available as a white, sterile freeze-dried powder for injection or infusion and the strength is 1,500 international in each ampoule.³

Pharmacokinetics

The clearance of hyaluronidase in the serum occurs with a $t_{1/2}$ of 2.1 ± 0.2 min. The drug is metabolized in the kidneys and liver. The effects are reversed within 48 h.⁴

Recombinant hyaluronidase

Prior to the introduction of a formulation derived from purified recombinant hyaluronidase, rHuPH20, the drug was derived from crude extracts of bovine testicular tissue. IgE-mediated allergic reactions used to happen on repeat administration. The latest hyaluronidase formulation to receive FDA approval, rHuPH20 (Hylenex), was introduced to decrease these adverse events.⁵

A study was conducted on recombinant human hyaluronidase. In this double-blind, placebo study, patients were injected with 0.1 ml of rHuPH20 intradermally in volar aspect of one forearm. In the other forearm 0.1 ml of normal saline was injected. There were no allergic manifestations observed among the 100 volunteer subjects. These findings supported the approval of the recombinant human hyaluronidase product.⁶

Uses

The clinical uses of hyaluronidase include, as an adjuvant added to increase the absorption of other injected drugs, for hypodermoclysis and as an adjunct in subcutaneous urography for improving resorption of radio-opaque agents. Other indications include in ophthalmic surgery, in combination with local anaesthetics.⁷

Chronic painful conditions such as radicular pain and/or lower back pain can be improved by lysis of adhesions. The aim is to remove barriers in the epidural cavity that are thought to contribute to the pain process and prevent the delivery of pain-relieving drugs to the target site. Hyaluronidase is used to facilitate removal of adhesions.⁸

Another off-label use of hyaluronidase is to reduce edema in various clinical conditions such as paraphimosis, intestinal intussusception, supraglottic airway edema and transplanted organ rejection.⁴

Use in anaesthesia

Local anaesthetics with additives have been used to prolong regional blockade. Vasoconstrictors can be used to constrict vessels, thereby reducing vascular absorption of the local anaesthetics.⁹ Many methods were used to reduce the total time to reach complete sensory block during supraclavicular block. These methods include increasing the injection volume or concentration of local anaesthetics, multiple injection techniques, combining different local anaesthetics, or adding additives such as dexamethasone, dexmedetomidine, clonidine, and magnesium to the local anaesthetics.¹⁰ Addition of hyaluronidase is another method to increase the spread of local anaesthetics so that onset time can be reduced.

Contraindications for the use includes its use as a drug to reduce the swelling of bites or stings or at sites where infection or malignancy is present.¹¹ Also in known hypersensitivity to hyaluronidase. Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs.

Hyaluronidase can be mixed with morphine, diamorphine, hydromorphone, chlorpromazine, metoclopramide, promazine, dexamethasone, local anaesthetics and adrenaline.

Pregnancy and lactation

The secretion of drug through breast is not known although it is unlikely to harm the breast-fed infant. Caution should be exercised in administering it to nursing mothers.

Hyaluronidase is physically compatible with 0.9% sodium chloride, 0.18% sodium chloride with 4% glucose, 0.45% sodium chloride with 2.5% glucose and 5% glucose. Electrolyte containing fluids are preferred and should be given too slowly.¹² Physical incompatibilities has been reported with heparin and adrenaline furosemide, benzodiazepines and phenytoin.

Undesirable effects

Hypodermoclysis has been associated with oedema formation.¹³ Allergic reactions have been reported when the drug is used with local anaesthetics in ophthalmology.

Severe allergic reactions have been reported rarely. Shelf life of the drug is 1 year and should be stored below 25°C.¹⁴

Special precautions for disposal and other handling

The prepared solution should be clear and should be used immediately after preparation. Common side effects include injection site reactions like pain, swelling and redness.

In a study, ninety patients received ultrasound-guided brachial plexus block through supraclavicular approach. They were divided into three groups. One group received lignocaine and 0.5% bupivacaine by triple-injection technique. Another group received 2% lignocaine and 0.5% bupivacaine plus 0.9% normal saline containing 900 IU (90 IU/ml) hyaluronidase triple-injection technique. The last group received 2% lignocaine and 0.5% bupivacaine plus 0.9% normal saline containing 900 IU (90 IU/ml) hyaluronidase by single-injection technique. The onset time for sensory and motor blockade was found to be lesser in the groups where hyaluronidase was added. Also it was found that hyaluronidase has no effect on the total analgesic duration and on the consumption of postoperative analgesics.⁷

In this prospective randomised double-blind trial, hyaluronidase was added to ropivacaine achieve for axillary brachial plexus block. There were two groups. The hyaluronidase group received ropivacaine 0.5% with 100 IU/ml of hyaluronidase, and the other group received ropivacaine alone. The hyaluronidase group had shorter sensory block onset time compared with the control group.¹⁵

In another study hyaluronidase was studied on its ability to provide pain relief in patients with lumbar radiculopathy. A sample of 252 patients who underwent an injection procedure with or without hyaluronidase due to radiculopathy were included in this study. The control group received triamcinolone 1ml ,0.25% bupivacaine and 1 ml normal saline and the study group received 1500 IU hyaluronidase. It was found that the control group had higher pain scores than the hyaluronidase group.¹⁶

In a randomized double-blind study, the lidocaine with epinephrine was compared with lidocaine with epinephrine and hyaluronidase in inferior alveolar nerve blocks. It was found that the group that received hyaluronidase had severe pain and trismus post operatively. Thus it was observed that hyaluronidase has the potential to cause tissue damage also and it should not be added to local anaesthetic solutions for inferior alveolar nerve blocks.¹⁷

Sixty CKD patients were evaluated for the effect of hyaluronidase as an adjuvant with bupivacaine in ultrasound-guided supraclavicular brachial plexus block. In group I, patients received plain bupivacaine 0.5% by single-injection technique while in group II, patients received plain bupivacaine 0.5% with 500 IU hyaluronidase. Hyaluronidase group had a significantly rapid onset of sensory and motor block than that of the bupivacaine group. Thus the findings of this study was similar to previous studies on nerve blocks and proves that hyaluronidase is an excellent adjuvant in nerve blocks.¹⁸

In another study patients undergoing elbow, forearm or hand received a single-injection axillary brachial plexus block with or without the addition of 150 Units rHuPH20 to a local

anaesthetic solution of bupivacaine, lidocaine and epinephrine. The success rate for the blocks were similar in both groups.¹⁹

In a study, 64 patients undergoing elective craniotomy operations were enrolled to receive scalp nerve block with 15 ml bupivacaine 0.5% and 15 ml lidocaine 2%, in 1:400000 epinephrine. The study group received additional hyaluronidase with the above combination. Results showed that patients in the H group showed lower VAS compared to the LA group. Thus it was proved that the addition of hyaluronidase to the local anaesthetic mixture improves the success rates of the scalp nerves block.²⁰

Thus most of the studies shows no evidence of undesirable effects in relation to the addition of hyaluronidase in local anaesthetic mixtures. The results of these studies could be attributed to the action of hyaluronidase in degrading hyaluronic acid, a basic component of extracellular tissue, resulting in spreading of local anaesthetic and a better.

Hyaluronidase injection is used as a preservative in combination with other medicines. It helps the medicine to absorb completely by the cells in the body and increases the potency of the medicine. It is a safe medicine and has minimal or no side effects.

Conclusion

Hyaluronidase has been successfully used for over sixty years. Studies have proved its effectiveness in spreading of local anaesthetics and the ability in dispersion of drugs. Also it was proved that there are no significant allergic manifestations or adverse events to the usage of drug. All injectable formulations generally have identical indications, activities and dosing.

As hyaluronic acid is found everywhere in the human body, the applications of this drug to facilitate the absorption of other drugs are vast and many off-label uses for hyaluronidase exist. Facilitation of epidural adhesiolysis and reduction of edema by hyaluronidase may be useful in treating radiating pain and lower back pain.

Reference

- 1) Jung H. *Hyaluronidase: An overview of its properties, applications, and side effects.* Arch Plast Surg. 2020;47(4):297-300
- 2) Messeha MM, Elhesy AE. *Comparison of orbital muscle akinesia caused by rocuronium versus hyaluronidase mixed to the local anesthetic in single injection peribulbar block for cataract surgery.* Anesth Essays Res. 2015;9(3):374-8.
- 3) Jung H. *Hyaluronidase; An overview of its properties, applications and side effects.* Vol.47, Archives of Plastic surgery. Georg Thieme Verlag; 2020.; 97-300.
- 4) Dunn AL, Heavner JE, Racz G, Day M. *Hyaluronidase: a review of approved formulations, indications and off-label use in chronic pain management.* Expert Opin Biol Ther 2010; 10:127–131.
- 5) Frost GI. *Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration.* Expert Opin Drug Deliv. 2007 Jul;4(4):427-40.
- 6) Yocum RC, Kennard D, Heiner LS. *Assessment and implication of the allergic sensitivity to a single dose of recombinant human hyaluronidase injection: a double-blind, placebo-controlled clinical trial.* J Infus Nur. 2007 ;30(5):293-9.

- 7) Hakim Karim Y kamal, Ahmed Mohamed Awad Al Saeid. Effect of addition of hyaluronidase as an adjuvant to local anaesthetics in ultrasound-guided supraclavicular brachial plexus block. *Ins Shams Journal of Anaesthesiology*.2017(10)213-218.
- 8 Racz GB, Heavner JE, Trescot A. Percutaneous lysis of epidural adhesions--evidence for safety and efficacy. *Pain Pract*. 2008;8(4):277-86.
- 9) Catherine J. Sinnott, Lawrence P. Cogswell, Anthony Johnson, Gary R. Strichartz; *On the Mechanism by Which Epinephrine Potentiates Lidocaine's Peripheral Nerve Block*. *Anesthesiology* 2003; 98:181–188.
- 10) Krishna Prasad GV, Khanna S, Jaishree SV. Review of adjuvants to local anesthetics in peripheral nerve blocks: Current and future trends. *Saudi J Anaesth*. 2020;14(1):77-84..
- 11) Murray G, Convery C, Walker L, Davies E. Guideline for the Safe Use of Hyaluronidase in Aesthetic Medicine, Including Modified High-dose Protocol. *J Clin Aesthet Dermatol*. 2021;14(8):69-75.
- 12)Vanessa Galuppo Brun..Hypodermoclysis: a literature review to assist in clinical practice. *Einstein*. 2015;13(1):122-8.
- 13) Adem S, AlMouaalamy N. Effectiveness and Safety of Hypodermoclysis Patients With Cancer: A Single-Center Experience From Saudi Arabia. *Cureus*. 2021;13(3):e13785.
- 14) King M, Convery C, Davies E. This month's guideline: The Use of Hyaluronidase in Aesthetic Practice (v2.4). *J Clin Aesthet Dermatol*. 2018 ;11(6):61-68.
- 15) Koh WU, Min HG, Park HS, Karm MH, Lee KK, Yang HS, Ro YJ. Use of hyaluronidase as an adjuvant to ropivacaine to reduce axillary brachial plexus block onset time: a prospective, randomised controlled study. *Anaesthesia*. 2015;70(3):282-9.
- 16) Ko SB, Vaccaro AR, Chang HJ, Shin DY. An evaluation of the effectiveness of hyaluronidase in the selective nerve root block of radiculopathy: a double blind, controlled clinical trial. *Asian Spine J*. 2015;9(1):83-9.
- 17) Ridenour S, Reader A, Beck M, Weaver J. Anesthetic efficacy of a combination of hyaluronidase and lidocaine with epinephrine in inferior alveolar nerve blocks. *Anesth Prog*. 2001;48(1):9-15.
- 18) Tarek A,Alaa M,Amayn F.Effect of hyaluronidases added to different concentrations of bupivacaine on quality of ultrasound-guided supraclavicular brachial plexus block. *Egyptian Journal of Anaesthesia*.2021(37)9-14.
- 19) Annelot C Krediet¹ , Nizar Moayeri² , Gerbrand J Groen³ , Aaron Hess⁴ and Paul E Bigeleisen. Hyaluronidase revisited: A comparison of axillary plexus block with and without recombinant human hyaluronidase. *Glob Anesth Perioper Med*.2015;(2): 62-64.
- 20) Mohamed AA et al. Safety and efficacy of addition of hyaluronidase to a mixture of lidocaine and bupivacaine in scalp nerves block in elective craniotomy operations; comparative study. *BMC Anesthesiol*. 2018;18(1):129.