Neuroplasty, previously known as percutaneous adhesiolysis, is an effective procedure for the treatment of refractory axial and radicular pain, failed back syndrome, and spinal stenosis (1). A systematic review found Level 1 evidence supporting neuroplasty for back and lower extremity pain (2). Subsequent to the systematic review, additional studies from Korea, looking at 169 patients over a 12-month follow-up, have shown neuroplasty's efficacy in spinal stenosis (3,4). A recent review of neuroplasty (5)
neuroplasty. There are ongoing differences in understanding of the definition of wound catheter, the authors believe that the use of a spring-wound catheter is inherent in the definition of epidural adhesions using solution injection (e.g., hypertonic saline, enzyme) or mechanical means (e.g., catheter) including radiologic localization...” While this definition does not mandate the use of a spring-wound catheter, the authors believe that the use of a spring-wound catheter is inherent in the definition of neuroplasty. There are ongoing differences in understanding as to where the catheter should be placed and which medications should be injected through it. The multiplicity of protocols used in the published studies regarding neuroplasty highlights this variation.

One of the points of variation in how neuroplasty is performed is whether and how to use hyaluronidase. A 2012 systematic review indicated that hyaluronidase did not improve outcomes in neuroplasty (8). A 2014 review found some support for using hyaluronidase (9). A 2017 editorial, which questioned whether the evidence supporting the use of neuroplasty was convincing, also questioned whether hyaluronidase should be used (10). A recent systematic review performed by methodologists looking at neuroplasty for failed back surgery syndrome noted that technical characteristics, including the use of hyaluronidase, varied by the individual practitioner (11). This Brazilian review indicated that no cost-effectiveness studies of neuroplasty had been performed for this indication. A randomized controlled trial (RCT) of neuroplasty for failed back surgery syndrome found that the cost-effectiveness of a one-year quality-of-life improvement was $2,080 (12).

The purpose of this current review is to assess the role of hyaluronidase in neuroplasty.

The review was performed via PubMed and Google Scholar searches of hyaluronidase and epiduroscopy or adhesiolysis until April 2019, review of the citations of relevant literature, and the authors’ knowledge of the literature and activity in the field. The literature was reviewed considering hyaluronidase’s physiologic role, allergenicity, medical uses, and evaluation specifically for neuroplasty.

Hyaluronidase has had multiple uses in medicine, including ophthalmic anesthesia, treatment of carpal tunnel syndrome, insulin absorption, subcutaneous infusion of IgG, and cancer treatment (13-17).

Hyaluronidase was first described by Duran- Reynals (18,19) at the Rockefeller Institute. Hyaluronidase is found in tissues such as the testes and in snake and bee venoms, with functions as diverse as enhancing sperm fertilization of eggs and the spreading of toxins (20,21). Hyaluronidase liquefies the interstitial barrier between cells, thus enhancing the spread of substances through the extracellular matrix. The primary mode of action is lysis of hyaluronic acid, although other components of the extracellular matrix are also substrates (22). Hyaluronic acid is a linear mucopolysaccharide consisting of alternating monosaccharides (23). Hyaluronic acid is a viscous lubricating substance with a high affinity for water. Hyaluronidase breaks hyaluronic acid into tetrasaccharides, allowing dispersion through the extracellular matrix, but not across fascial planes.

Hyaluronidase continues to be effective when combined with the medications used in interventional procedures (24).

The use of hyaluronidase as an adjunct to pain management procedures was first reported by Moore (25) in 1950. Moore found that hyaluronidase was most effective in procedures involving infiltration of subcutaneous tissues, such as hernia repairs.

There has been considerable interest in the use of hyaluronidase since Moore’s pioneering work. Geurts and McCleane (26,27), in uncontrolled studies, reported good relief from caudal injections and epiduroscopy using hyaluronidase.

Yousef et al (28) performed an interesting prospective, randomized, double-blinded study on failed back patients comparing 40 mL caudal injections, without a catheter, of local anesthetic, steroid, and 3% saline with and without hyaluronidase. Only the hyaluronidase group had significant relief at one year. Choi et al
There have been no reported cases of allergic reaction to hyaluronidase since the transition to the recombinant preparation (39).

Two independent laboratories, in Brazil and China, have independently shown that hyaluronidase does not elicit an immune response. Fronza et al (40) showed that bovine hyaluronidase had anti-inflammatory potential, inhibiting cellular recruitment, edema formation, and pro-inflammatory mediator production; and suggested that hyaluronidase could be used to decrease the effects of acute inflammation. Huang et al (41) found that recombinant hyaluronidase had lacked the ability to generate inflammation and inhibit inflammation by inhibiting neutrophil infiltration. Rosengren et al (42), in a manufacturer-funded study, found that recombinant human PH20 hyaluronidase induced only modest immunogenicity, which had no association with adverse events.

There is currently no recommendation that skin testing be performed prior to the use of hyaluronidase.

Hyaluronidase has no known adverse effects in the human body. Birkenmaier et al (43) evaluated the effects of bupivacaine, hyaluronidase, a corticosteroid, and hypertonic saline on fibroblast proliferation. Hyaluronidase had no effect on fibroblast proliferation. Schulze, in another in vitro study, found that hyaluronidase was effective with all combinations of drugs used in neuroplasty (44).

Hyaluronidase is safe when administered intrathecally. There is extensive experience reported from Bangalore spanning years regarding the intrathecal use of hyaluronidase to treat arachnoiditis caused by both tuberculous and by noninfectious etiologies (45-47). In like manner, perineural injection of hyaluronidase did not affect the myelin or axons (48).

A recent prospective trial from Croatia of neuroplasty using hyaluronidase and normal saline for both failed back surgery syndrome and lumbar radiculopathy concluded that neuroplasty with hyaluronidase and steroid should be the first treatment choice in these patients after conservative therapy, as the procedure was simple, safe, and effective (49).

The question of the role of hyaluronidase in neuroplasty was specifically evaluated by Heavner et al (50) in 1999. Eighty-three patients with low back and leg pain and with a filling defect on epidurogram were randomized to have neuroplasty with 4 treatment regimens: hyaluronidase and hypertonic saline, hypertonic saline, isotonnic saline, and hyaluronidase and isotonic saline. At 12 months, the hyaluronidase and hypertonic saline resulted in the greatest improvement in pain...
score and the Short Form McGill Pain Questionnaire. Further, the hyaluronidase/hypertonic saline group had the fewest number of procedures. Thus, the use of hyaluronidase and hypertonic saline had both the greatest benefit and the fewest interventions, compared to hypertonic saline alone or isotonic saline with or without hyaluronidase.

**Limitations**

While the efficacy of hyaluronidase has been documented (2), most irrefutably by Gerdesmeyer et al’s (34) randomized controlled trial, there have been limited studies examining the enhanced efficacy of neuroplasty when hyaluronidase is added.

**Conclusion**

Hyaluronidase acts by breaking down the viscous mucopolysaccharides in the interstitial matrix, allowing the greater spread of substances injected into the matrix. It is safe in the human body and has been widely used in medicine, including in the subarachnoid space. Recombinant hyaluronidase has been shown to not cause an immune reaction. There is no need to perform a skin test prior to using hyaluronidase.

Two high-quality studies have shown the effectiveness of the addition of hyaluronidase to neuroplasty procedures, with one of the studies specifically looking at whether the addition of hyaluronidase improved outcomes. Several other lower-quality studies have shown benefit from adding hyaluronidase to a variety of pain management procedures.

Hyaluronidase has been shown to be safe and effective in neuroplasty. Because of enhanced efficacy and safety and because of the decrease in the number of additional procedures, hyaluronidase should be considered for all neuroplasty procedures.

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**References**


16. Wasserman RL. Overview of recombinant human hyaluronidase-facilitated subcutaneous infusion of IgG in primary immunodeficiencies. *Immunotherapy*
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