Decompression of an Experimental Compartment Syndrome in Dogs with Hyaluronidase

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The treatment of compartment syndromes in which elevation of intracompartmental pressure occurs is by surgical fasciotomy. This is a relatively simple procedure but may be associated with complications. This study aimed at developing an alternative method to decompress a compartment by use of the enzyme hyaluronidase. Autologous plasma was infused into the anterolateral leg compartments of six dogs to simulate compartment syndromes of 80 mmHg. Pressure decay after pressurization was recorded. The compartment pressures were then again raised to 80 mmHg by subfascial injections of 1500 units hyaluronidase in 2 ml saline injected into one compartment and 2 ml saline only into the control side. Pressure decay was again recorded. On the experimental side, a significantly faster decay rate occurred after hyaluronidase injection than after initial pressurization; 8.0 ± 1.3 (S.E.M.) versus 3.4 ± 0.4 (S.E.M.) mmHg/min (p < .01). Pressure decay after hyaluronidase injection was significantly faster than after the same volume injection on the control side, over both a four-minute period (8.0 ± 1.3 [S.E.M.] versus 4.1 ± 0.6 [S.E.M.] mmHg/min [p < .03]) and a 25-minute period (2.1 ± 0.3 [S.E.M.] versus 1.3 ± 0.1 [S.E.M.] mmHg/min [p < .03]). Hyaluronidase removes hyaluronic acid molecules from the leg compartment fascia and, by facilitating fluid flow from the compartment, causes decompression. Hyaluronidase may then have a place in the prophylaxis and treatment of compartment syndrome, thus avoiding anesthesia and surgery.

Patients with acute and chronic compartment syndromes have elevated intracompartmental pressure and frequently require decompression by fasciotomy. Technically, fasciotomy is a relatively simple procedure, but it requires anesthesia, may decrease muscle function, and leaves a wound that usually necessitates a second operation for closure (often with addition of a skin graft). The patient then remains with scars at the fasciotomy and the requisite skin graft donor sites. In patients with underlying tibial fractures, fasciotomy makes fracture management more difficult. The development of a technique for treatment of compartment syndromes that avoids anesthesia and operative intervention but achieves as effective decompression as surgical fasciotomy would be an advance. This study aimed at such an approach by use of a subfascial injection of hyaluronidase.

METHOD

Six adult dogs, weighing 20–25 kg, were premedicated with xylazine (2 mg/kg), anesthetized with ketamine (25 mg/kg), and placed supine with their legs symmetrically arranged over a foam rubber support (Fig. 1). Continuous replacement saline therapy was maintained by an intravenous line, and the blood pressure, monitored by a brachial artery line, was kept at normal level.
Wick catheters were inserted into the proximal and distal ends of the anterolateral compartment of each leg, and basal pressures were measured on an eight-channel strip-chart recorder (Model 7418A, Hewlett-Packard, Palo Alto, California). Autologous plasma at 37°C was then infused into the midsubstance of the compartment musculature via an 18-gauge needle to achieve an intracompartmental pressure of 80 mmHg. The infusion was then stopped, and pressure decay was monitored down to 50 mmHg, which occurred in about ten minutes. Subfascial injections were then made simultaneously at proximal and distal sites in each anterolateral compartment: 750 units hyaluronidase (“Wydase,” Wyeth Laboratories Inc., Philadelphia, Pennsylvania) dissolved in 1 ml 1% methylene blue-saline solution were injected at each site into the experimental leg, and 1 ml of 1% methylene blue-saline only was injected at each site on the control side. Thus, each compartment received 2 ml of dyed saline, and one compartment additionally received 1500 units of the enzyme. These injections raised the intracompartmental pressures back to approximately 80 mmHg. The needles were left in situ, with syringes attached, thus preventing fluid flow through the needle puncture holes. The rate of pressure decay was again measured for about one hour, part of which is shown in Figure 2. At the end of the study, the animal was killed and the legs dissected to note the exact site of injection of the methylene blue. The slope of the pressure decay curve after initial pressurization was compared with the decay curve after methylene blue injection, with and without hyaluronidase, on the experimental and control side, respectively. Experimental and control decay curves were also compared with each other after methylene blue injection, with and without hyal-
Hyaluronidase. Mean decay rates were evaluated for significant (p < .05) differences by the paired Student's t-test.

RESULTS

At the conclusion of the experiments, examination of the dissected legs for intensity and location of the dye revealed that all methylene blue injections were subfascial and also partly infiltrated the underlying muscle. In all animals there was also a diffuse light blue staining of the subcutaneous tissues in the vicinity of the subfascial injection on the experimental side only.

On the control side, no significant difference (p > .5) was found between the pre- and postmethylene blue injection decay rates: 4.2 ± 0.7 (S.E.M.) versus 4.1 ± 0.6 (S.E.M.) mmHg/min (Fig. 3). On the experimental side, pressure decay for the four minutes following hyaluronidase injection was significantly faster (p < .01) than the decay before hyaluronidase treatment: 8.0 ± 1.3 (S.E.M.) versus 3.4 ± 0.4 (S.E.M.) mmHg/min (Fig. 3). There was no significant difference (p > .5) between the premethylene injection decay rates on the control and experimental sides. Pressure decay after hyaluronidase-saline injection was significantly faster than the rate after saline only, over both a four-minute period ([p < .03]: 8.0 ± 1.3 [S.E.M.] versus 4.1 ± 0.6 [S.E.M.] mmHg/min) and a 25-minute period ([p < .03]: 2.1 ± 0.3 [S.E.M.] versus 1.3 ± 0.1 [S.E.M.] mmHg/min) (Fig. 4).

DISCUSSION

Hyaluronidase is an enzyme widely distributed in nature, but it is principally obtained from bovine testicular tissue. The enzyme can act as a spreading and diffusing factor that modifies the permeability of connective tissue by the hydrolysis of hyaluronic acid. This acid exists as a gel and is one of the chief ingredients of the connective tissue “cement” that binds the collagenous fibers together. The spaces between collagen fibrils of fascia are approximately 50 μm in
The fascia enclosing the anterolateral leg compartment consists of a fabric of collagen fibers, with contained fibroblasts, bound together by a matrix of predominantly hyaluronic acid molecules that "waterproof" the membrane. In this study, the rheologic effect of the hyaluronidase occurred rapidly by removing the hyaluronic acid molecules and hence their "waterproofing" effect. Intra-compartmental fluid then passed through the fascia, as evidenced by the subcutaneous methylene blue staining, facilitating decompression of the compartment. Intracompartmental fluid pressure and arterial pulsations were considered to be the forces promoting the fluid passage through the fascia.

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Because the animals were anesthetized, muscular activity had no effect on the dynamics of the fluid flow.

Although the direct effect of hyaluronidase on skeletal muscle has not apparently been studied, beneficial effects of this enzyme on ischemic myocardium have been demonstrated when the enzyme was administered intravenously. It is postulated that hyaluronidase may improve the transport of nutrients to ischemic myocardium, enhance the "washout" of toxic metabolites accumulating during ischemia, and increase collateral blood flow to the area, probably by decreasing myocardial edema. Edema may be reduced by venous dilatation and reduced capillary pressure, thus shifting the Starling equilibrium to greater transcapillary resorption of tissue fluid. Hyaluronidase may also reduce resistance to flow in the interstitial space and speed reabsorption of edema fluid. Hyaluronidase also preserves intracellular glycogen stores in ischemic tissue and protects the microvasculature, thus improving collateral flow. Thus, if subfascial injection of hyaluronidase is used to reduce intracompartmental pressure, any incidental intramuscular injection would not be expected to adversely affect the skeletal muscle, which is somewhat similar to myocardial muscle.

Macromolecular substances, when perfused through a hyaluronidase-treated fascial membrane, slow saline flow through the membrane as the molecules accumulate in the interstices of the collagen network. Diluted serum acts in this fashion. Thus, it may be cautioned that the effect of hyaluronidase in lowering intracompartmental pressure may be temporary as larger molecules contained in the interstitial fluid effect a "rewaterproofing" of the fascial membrane.

Hyaluronidase is a nontoxic substance in even 500 times the maximal dose. It has been in medical use for many years, and while hypersensitivity to the enzyme occasionally occurs, no significant immune reactions to it have been reported. The enzyme has been used to increase the rate of absorption of fluids given by hypodermoclysis usually in children, when small or inaccessible veins make venipuncture especially difficult. In this case, the rate of fluid absorption may be increased three- to 12-fold by the addition of hyaluronidase to the infusant. When administered as a cone injection in glaucoma, hyaluronidase causes a temporary drop in intraocular pressure. The combination of hyaluronidase with nonabsorbable forms of steroid preparations for periarticular injections enhances the anti-inflammatory effect by facilitating spread of the steroid throughout the collagenous tissue. Hyaluronidase has also been used as an adjunct in subcutaneous urography for improving resorption of the radiopaque agent.

As this study has shown in a well-tested although not perfectly comparable animal model, hyaluronidase appears to have potential for rapidly alleviating pathologic intracompartmental pressures. The enzyme may therefore have a place in the treatment of clinical compartment syndromes where it could be used to perform a "chemical fasciotomy" and hence avoid anesthesia and surgery. In this respect, the use of hyaluronidase has some similarities to the systemic infusion of mannitol to lower intracompartmental pressure. However, in the case of raised intracompartmental pressure caused by continued arterial bleeding, the transport of fluid across the compartment fascia might lead to such an accumulation subcutaneously that skin compliance would be exceeded and no further lowering of intracompartmental pressure would occur. Hyaluronidase activity continues for several hours, but repeat injections could be performed if the source of raised intracompartmental pressure persisted for a longer period of time. Hyaluronidase injection, being such a simple and benign procedure, might also be used prophylactically when a compartment syndrome is anticipated. Nevertheless, controlled human studies are indicated prior to instituting clinical use of this enzyme.
REFERENCES


