The Cosmetic Use of Botulinum Toxin

Rungsima Wanitphakdeedecha, M.D., Woraphong Manuskiatti, M.D.
Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700. Thailand

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Introduction

Botulinum toxin is derived from the obligate anaerobic bacterium called *Clostridium botulinum*. Currently, there are eight subtypes of botulinum toxin (A, B, C1, C2, D, E, F, and G) which vary from approximately 300 to 900 kd in size, but only two subtypes (A and B) are manufactured for commercial use. All botulinum toxin subtypes can relax muscles by preventing the presynaptic release of the neurotransmitter acetylcholine (ACh) at the peripheral cholinergic motor neuron end plate. All botulinum toxin subtypes target one or more specific intracellular proteins necessary for synaptic release of neurotransmitter. Over time, the nerve-ending may sprout additional axons that establish new motor end plates. This results in a gradual return of motor function.

Botulinum toxin A is the most potent of all the subtypes and the most frequently used clinically. Its effects are both dose dependent and reversible. Muscle weakness can be demonstrated as early as 6 hours after exposure. However, full paralysis and obvious clinical effects usually reveal by 7 days, and last from 3 to 6 months. Physiologic and clinical effects disappear when new neuromuscular junctions develop and axonal sprouting takes place. The FDA approved botulinum toxin A (Botox®) for cosmetic use as treatment of glabellar hyperdynamic lines in 2002.

The Product

Nowadays, there are three botulinum toxin formulations commercially available, two of the A subtype; (a) Botox (Allergan, Irvine, Calif.) and (b) Dysport (Speywood Pharmaceuticals, Maidenhead, England; Inamed, Santa Barbara, Calif.), and one of the B subtype, Myobloc (Elan Pharmaceuticals, South San Francisco, Calif.). In Thailand, there are only two commercially available of botulinum toxin A.

Both Botox® and Dysport® come in a lyophilized form as a powder in a vacuum-sealed bottle. In this form, it is stable for approximately 4 years. It should be stored frozen at -5°C reconstituting with normal saline. The toxin is very sensitive to mechanical stress, heat, and pH, so care must be taken during reconstitution not to cause excessive heating or turbulence. Therefore, it is useful to avoid severe bubbling or shaking. After reconstitution, it may be refrigerated at 2-8°C. Efficacy of botulinum toxin can be decreased by low concentrations of toxin and by chemicals in the diluent. The manufacturers recommend reconstituting in 1, 2, or 4 mL sterile, non-preserved normal saline for a final concentration of 10, 5, or 2.5 units per 0.1 mL, respectively.

For the most clinical efficacy, the manufacturers recommend clinicians using botulinum toxin within 4 hours after reconstitution and unused toxin should be refrigerated. However, some in vivo studies suggest that potency may last as long as 6 weeks if properly refrigerated. Importantly, the efficacy of the botulinum toxin will be destroyed by refreezing the toxin. The toxin also has decreased effect with time after reconstitution. The amount of diminished effect reported varies greatly, but roughly 50% of the effect may remain after 1 week.

Techniques of Botulinum Toxin Application

Many clinicians prefer to reconstitute the final botulinum toxin in a 1-mL syringe with a 30-gauge needle to minimize the pain of injection. Some prefer hubless needles so that no toxin is wasted in the hub, whereas others add an additional 0.2 mL of saline to compensate for the volume of solution that is lost in the hub.

Facial wrinkles are frequently due to repeated muscle contraction. Botulinum toxin A can treat facial rhytides by producing weakness or paralysis of these muscles. To acquire these cosmetic purposes, botulinum toxin should be injected directly into the desired muscle which could be identified by having the patient contract the muscle, causing the formation of rhytids. Then, botulinum toxin A will weaken the overactive underlying muscle contraction, causing a flattening of the facial skin and an improved cosmetic appearance. The larger the treated muscles, the higher doses of toxin to produce an effect are required. Generally, male patients require higher doses than females.

The effect of botulinum toxin is only temporary, but it has a very low incidence of side effects as well. In order to decrease the side effects, the needle should be pointed away from the globe during the injection, and the patient should be instructed to remain in the upright position for 4 hours after the injection. Immediately after injection, movement of the treated muscles is encouraged so that the toxin is taken-up by the involved neural endplates. Patients should repeat the treated muscle movement ten times per hour for the first 4 hours.

Complications

Complications of botulinum toxin in cosmetic use may

be local, immunologic, or unrelated to the toxin itself. Local complications can occur at any site of injection including pain, edema, erythema, ecchymosis, headache, and short-term hypesthesia. The most common local complication is ecchymosis which occurs easily in the soft eyelid tissue and can be minimized by applying pressure at the injection site immediately following needle withdrawal. Moreover, ecchymosis can be minimized by avoiding aspirin, aspirin-containing products, and products that inhibit platelet function (nonsteroidal antiinflammatory agents) for 7 to 10 days before injection. Limiting the number of injections will assist in reducing the frequency and severity of bruising.

Injection techniques are also helpful in reducing pain. Pinching the skin and the underlying muscle, slowly inserting the needle bevel up through the opening of a pilosebaceous unit, and slowly injecting the solution will also help to diminish discomfort. Ice applied immediately after injection will further reduce the pain as well as the edema and erythema associated with injection.

Immunogenicity and neutralizing antibodies have not been reported in cosmetic and functional oculofacial use of botulinum toxin. Antibodies are thought to be related to both dose and frequency. In addition, it often requires more than 300 units injected at 1 session at a frequency of at least every 3 months. To reduce the immunigenicity of botulinum toxin, the current batch of botulinum toxin A has 80% less protein than the previous batch.

Lethal dose or the lethal dose botulinum toxin for 50% (LD_{50}) is defined for mice as one unit. The LD_{50} for humans is estimated to be 40 units/kg, or approximately 2,800 units for a 70-kg man. This dosage far exceeds the amount used clinically in cosmetic purposes.

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