The Application of Botulinum Toxin in Oral and Maxillofacial Surgery

Edited by
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Preface

Botulinum toxins are proteins which are highly effective, naturally occurring neurotoxin, produced as a metabolic product of the gram-positive bacteria, Clostridium botulinum. Botulinum toxin, once a food poison, was later exploited as a biological weapon, and is currently one of the most versatile pharmaceuticals for the treatment of human diseases in ophthalmology, neurology, dermatology and oral and maxillofacial surgery.

Application of this toxin drug in the field of oral and maxillofacial surgery for both aesthetic and functional indications has been extensively reported. However, a collective documentation of its varied applications is lacking. This book is a compilation of the use of botulinum toxins in head and neck surgery and medicine. The book also covers the basic aspects of the drug, including its history, pharmacology and preparation. Dermatological applications of the drug for cosmetology, as well as its various therapeutic uses in temporomandibular joint surgery, masseter muscle hypertrophy, bruxism, trismus, maxillofacial traumatology, salivary gland diseases, facial palsy, trigeminal neuralgia and gummy smiles have been described with numerous clinical and diagrammatic illustrations. The book will find relevance with head and neck surgeons, oral maxillofacial surgeons, ENT surgeons, and dermatologists in particular and also general surgeons and dentists as well.

Chapter 1

Introduction: Know the Toxin

Kumar Nilesh, Monica Patil

The history of medicine indicates unexpected coincidences leading to the development of treatment options. One of these serendipities was the discovery of the clinical application of botulinum toxin. Botulinum toxin, once a food poison, was later exploited as a biological weapon during World War II. Currently, it is one of the most versatile pharmaceutical agents used for the treatment of human diseases in ophthalmology, neurology, dermatology, dentistry, and oral and maxillofacial surgery. Botulinum toxin is a protein, which is a highly effective naturally occurring neurotoxin. It is produced as an ametabolic by-product of the gram-positive, obligate anaerobic, rod-shaped bacteria *Clostridium botulinum* (Figure 1A).

Botulinum toxin is a two-chain polypeptide. It consists of a light chain and a heavy chain, joined by a di-sulphide bond. Botulinum toxin formed from Clostridium botulinum is initially a single chain. The biologically active form of botulinum toxin is formed after the enzymatic splitting (nicking) of the progenitor toxin molecule by the process of proteolysis. This results in the formation of the active two-chain form of botulinum toxin (Figure 1B). The heavy chain provides specificity of the botulinum toxin molecule to the cholinergic receptors. It brings about the binding of the toxin molecule at the pre-synaptic cholinergic receptors, preventing the action of acetyl cholinesterase in impulse transmission across the synaptic junction.

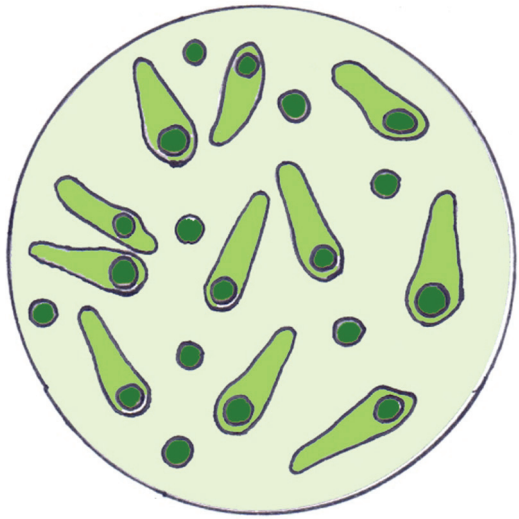

Figure 1A: Microscopic appearance of gram-positive, rod-shaped bacteria Clostridium botulinum

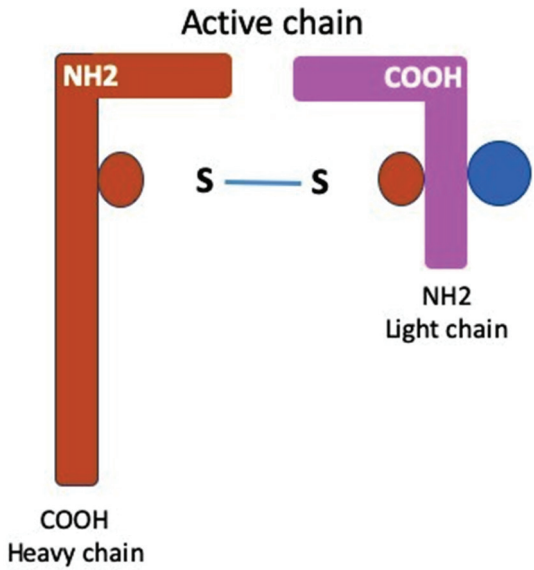

Figure 1B: Line diagram showing structure of botulinum toxin

Botulinum toxin exists in seven distinct serological forms: A, B, C (C_1, C_2), D, E, F and G. Although all the types are structurally similar, they vary serologically and antigenically. The various serotypes differ in their duration of effect and potency. Type A is the most potent neurotoxin, followed by types B and F.

Type B was probably the first botulinum toxin serotype discovered, when investigation of an outbreak of food poisoning called *botulism* in Belgium, in 1895, revealed that the causative agent was a neuroparalytic toxin produced by an anaerobic bacterium.[1] Several years later a similar incident occurred in Germany, and the bacterium was isolated. Although the bacteria that produced the two toxins were similar, as were their paralytic effects, the antisera against either toxin were not protective against the other, indicating that the two toxins were immunologically distinct. It is believed that the toxin identified in Germany was type A.[2] Type A neurotoxin is the most effective and has the longest duration of action. It is the main serotype in therapeutic use, both for aesthetic and therapeutic indications.

Botulinum toxin acts by inhibiting the exocytotic release of acetylcholine from the motor nerve terminals. Because of this property, it has been found useful in the treatment of many pathological conditions that involve excessive muscle contractions. Botulinum toxin was first developed as a therapeutic agent for the treatment of disorders that cause localized muscle hyperactivity, especially around the eyes. Ophthalmologists and neurologists were quick to appreciate the fact that botulinum toxin treatment improved the disfigurement, discomfort and disability that are associated with facial dystonias. Further investigations on botulinum toxin revealed significant benefit in pain control resulting in improvement in muscle contractions which was not associated with its neuromuscular effects. This suggested that the toxin might have an effect on pain which is independent of its neuromuscular actions.[4] Similarly, in the late 1990s, the effects of botulinum toxin were examined on the hyper-functional lines of the face.[5] Cosmetic surgeons who were using botulinum toxin for aesthetic purposes were the first to notice that in certain patients, the facial injections of the toxin also provided relief from tension and migraine headaches, making it one of the most exciting areas of botulinum toxin research.[6] In clinical practice, botulinum toxin has an excellent safety profile when used in minute quantities by experienced clinicians.

Over the past few decades physicians have constantly discovered new applications for this drug and new ways to refine its use. It has been used in various fields of both medicine and surgery. This book describes the therapeutic as well as cosmetic applications of botulinum toxin in general, with specific focus on the fields of oral and maxillofacial surgery, facial aesthetics, dermatology, and dentistry.

Learning points:
▪ Botulinum toxin are proteins which are highly effective, naturally occurring neurotoxin, produced as a metabolic product of the gram-positive, obligate anaerobic, rod-shaped bacteria, Clostridium botulinum.
▪ It is a two-chain polypeptide consisting of a light chain and a heavy chain, joined by a di-sulphide bond. Initially as single chain (precursor toxin), the final active form of the protein is a complex makeup of the two-chain neurotoxin.
▪ Botulinum toxin exists in seven distinct serological forms (A to G). These serotypes differ in their duration of effect and potency. Type A is the most potent with the longest duration of action and is most widely used for cosmetic and therapeutic purposes.
▪ Botulinum toxin, first developed as a therapeutic agent for the treatment of disorders that cause localized muscle hyperactivity, later showed significant benefit on pain and on hyper-functional lines. It finds both therapeutic and cosmetic use in the fields of oral, dental and maxillofacial surgery.

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Chapter 2

History of Botulinum Toxin: From Bane to Boon

Monica Patil, Kumar Nilesh

Since the beginning of time, humankind has been affected by several food-borne ailments. Since the time humans started preserving and storing food, it has created an optimal condition for the presence and growth of Clostridium botulinum (for example, in France ham was stored in the barrels of brine, in the Baltic poorly dried herring, in Scandinavia trout was packed in willow baskets to ferment, non-salted sturgeon roe were piled in a heap on old horsehides, lightly smoked fish in poorly heated smoking chambers, and liver sausages swung from the rafters of Austrian huts).[1] In ancient times, correlation between food consumption and subsequent death from a paralytic disease was not realized. Therefore, there are very few sources and documents available on food poisoning before the 19th century. However, some knowledge from ancient dietary laws and taboos considered the consumption of poisoned food as life-threatening. Louis Smith, in the year 1977 reported one such example of dietary taboo that was reported in his textbook on Botulism.[2] At first, this food poisoning was suspected to be atropine intoxication. However, in the old medical literature, some reported cases of intoxication with Atropa belladonna were in fact said to be cases of food-borne botulism. This was because the combination of dilated pupils and fatal muscle paralysis could not be attributed to atropine intoxication.[3]

The accurate clinical symptoms of food-borne botulism were described and published by a German physician, Justus Kerner, between the years 1817 and 1822. The idea of using botulinum toxin for therapeutic measures was also developed by him. He also described and categorized this empirical phenomena and started clinically experimenting on animals and on himself and succeeded in developing the hypotheses on the toxin‘s pathophysiology,

suggesting preventive measures and the treatment of botulism. Along with this, Kerner also developed the vision and ideas of future perspectives and therapeutic uses of the toxin which have been validated over the last 20 years.

1792–1815 (Southern Germany)

During the Napoleonic wars, general economic poverty was experienced in the rural areas of central Europe because of the devastating warfare by the French, which resulted in a decline in the hygiene of everyday life, including food production. In the early 19th century, an increasing number of lethal food poisoning cases were registered by the medical administration of the Dukedom, followed by a notice that was published by the government of Stuttgart to alert the population on the harmful consumption of smoked blood sausages.

In 1811, the medical section of the Internal Affairs Department of the government of Stuttgart suspected the probable cause of sausage poisoning to be prussic acid. Later, with the involvement of the medical faculty of the University of Tü bingen, it was stated by the dean (Professor Wilhelm Gottfried von Ploucqet) that prussic acid could be a zoonic, probably organic poison. Systemic studies were then initiated on this issue by the government of Württemberg, after a medical professor (Johann Heinrich Ferdinand Authenrieth) of the University of Tü bingen suggested that further outbreaks of food poisoning should be very well recorded. He also held the local housewives responsible for inadequately boiling sausages during food preparation, resulting in them rotting from the inside.

In 1815, seven cases of intoxication were reported after liver sausage and pea ingestion. The autopsy findings of the three victims in this incident were described by a health officer (J.G. Steinbuch) in Herrenberg, Stuttgart. Another case of food poisoning was reported in the same year by a physician (Justinus Kerner), that revealed the probable cause to be various kinds of sausages. After these reports, in 1817 Professor Authenrieth decided to publish them. Subsequently, Kerner observed 76 cases, which he published in his first monograph, entitled “Neue Beobachtungen über die in Württemberg so häufig vorfallendentö dlichen Vergiftungen durch den Genuss geräucherter Würste” (“New observations on lethal poisoning occurring so frequently in Wurttemberg through the consumption of smoked sausages”). He

stated that the toxin interrupts chemical processes of nervous transmission, in the same way as rust stops conduction of electricity.[4] He then received a grant from the government of Stuttgart that helped him to escalate his research and start an animal study in 1821. He started his study by extracting the lethal substances from sausages and similar products and calling it *sausage poison*. He used this poison by mixing it with honey and then fed it to various animals, such as cats, rabbits, birds, frogs, snails, and insects such as locusts and flies. The observed clinical symptoms, particularly in cats, were very much alike those occurring in humans. As there were no observations showing disturbances in consciousness, he concluded that the poison did not affect the brain and described it as only having muscular and autonomic symptoms. The action of the toxin was observed to be in the peripheral sympathetic and parasympathetic nerves and its signal interruption, without any sensory disturbances. However, poisoning also showed lethal outcomes in autopsies, such as secondary respiratory and cardiac failure. Kerner also dauntlessly experimented on himself by ingesting a few drops of this sour poison, after which he experienced mild symptoms of sausage poisoning, such as the drying out of his tongue, palate, and pharynx in a short period of time. In 1822, he published his second monograph entitled "Das Fettgiftoder die Fettsa¨ureundihre Wirkungen auf den thierischen Organismus, ein Beytragzur Untersuchung des in verdorbenen Wu¨rstengiftigwirkenden Stoffes." (Fat poison or fatty acid and its effects on the animal organism: A contribution to the examination of poisonous substances from bad sausages), reporting the clinical evaluation of no less than 155 cases, including human autopsies, animal experiments, and all the knowledge he had gathered so far. He mentioned very interesting clinical details: "the tear fluid disappears, the gullet becomes a dead and motionless tube; in all the mucous cavities of the human machine the secretions of the normal mucus stand still, from the biggest, the stomach, towards the tear canal and the excretory ducts of the lingual glands. No saliva is secreted. No drop of wetness is felt in the mouth, no tear is secreted anymore".

The main clinical symptoms that he described were: vomiting, intestinal spasms, mydriasis, ptosis, dysphagia, and finally, respiratory failure.[5] After comparing various sausage recipes, Kerner found the common ingredients to be fat and salt. However, salt was supposed to be known as being innocent, hence, it was

assumed that the toxic changes were because of the fat, after which the denomination for the toxin; *"fat poison"* was established. This 'new poison' was concluded to be of zoonic origin, as it developed under anaerobic conditions in rotten sausages, after comparing its mode of action with the already known poisonous substances, such as atropine, scopolamine and snake venom. It was also concluded that its action was on the nervous system and that it was lethal even in small doses. Kerner repeatedly suggested storing the sausages in dry conditions to prevent further incidents of poisoning. In the final statements of his second monograph, Kerner discussed the toxin as a possible remedy for a variety of diseases, favoring a condition known as "Veitstanz" (St. Vitus dance, comparable with chorea Huntington and chorea minor) or the hyper-secretion of body fluids. More than 180 years ago, Kerner presumed that his statement on 'fatty acid' as a therapeutic agent belonged to the realm of hypothesis and may be confirmed or disproved by observations in the future.[1, 6, 7] In the 1870s, more than 50 years later, the term 'botulismus' was derived from the Latin word botulus for sausage.

1895 (Belgium)

Almost 80 years after Kerner's work, when 34 musicians of "Fanfare Les Amis Réunis" – a local brass band, relished on pickled and smoked ham at the funeral of 87-year-old Antoine Creteur in the Belgian village of Ellezelles, they all developed mydriasis and diplopia, and some of them also developed dysphagia and muscle paralysis, which led to three of them dying. The microbiologist Emile Pierre Van Ermengem, professor at the University of Ghent, formerly trained by the famous Robert Koch in Berlin, examined the ham and carried out autopsies and became the first to find the correlation of *'sausage poisoning'* with a bacterium found in the tissues of the contaminated victims and raw salted pork. In 1897, in his report on this anaerobic, spore-forming, toxin-producing bacillus, he named it Bacillus botulinus, as the term botulismus was already known at this time.[8] Subsequent investigations further discovered different serological subtypes. In the later years, van Ermengem's bacillus was renamed as Clostridium botulinum.[9]

World War II: botulinum toxin as a biological weapon

In the 1920s, a crude preparation of botulinum toxin was obtained by Herman Sommer, at the University of California by acidic preparation of a culture fluid. This was used by the US Academy of

Sciences at the beginning of World War II in a secret laboratory in Fort Detrick, Maryland. For this purpose, physicians and bacteriologists were deployed to investigate the bacteria and toxins that could be used. During this time, the United States Office of Strategic Services came up with a plan of using Chinese prostitutes as assassins for the Japanese high ranking army officers by smuggling lethal doses of botulinum toxin into their drinks or food in a pin-size gelatin capsule. These capsules were sent to Chunking, China, where they were again tested on stray donkeys before executing the program. However, the donkeys survived and the plan was abandoned. Later, it was found that donkeys could be one of the few species that were immune to botulinum toxin.[10] The first botulinum toxin for human use was produced by Edward Schantz, a scientist at Fort Detrick, in 1946. In 1972, the Biological and Toxic Weapons Convention was signed by Richard Nixon (US president) that terminated all research on biological agents used in warfare.

Medical research

After multiple unsuccessful attempts to treat strabismus, by injecting various substances into the hyperactive muscles, Alan Scott, an ophthalmologist at the Smith-Kettlewell Eye Research Institute, San Francisco, approached Edward Schantz for the botulinum toxin. In 1978, Scott received permission from the FDA to conduct a pilot study on human volunteers for the treatment of strabismus.[11] The FDA then approved the use of botulinum toxin type A, to a certain extent, in humans by 1979. Botulinum toxin effectively blocked involuntary muscle contractions, when it was injected into the larger muscles of the body. Later, in 1989, the FDA approved the use of botulinum toxin-A for hemi-facial spasms, strabismus and blepharospasms. In 1987, after injecting botulinum toxin for blepharospasm, Jean Carruthers, a Canadian ophthalmologist, observed that frown lines disappeared. She shared the same with her husband, Alastair Carruthers, who was a dermatologist. After this accidental observation, the Carruthers revolutionized aesthetic enhancement treatments by promoting botulinum toxin in cosmetic procedures and published their first report on botulinum toxin application for cosmetic purposes in 1996.[12] Since then, numerous new indications have been found after various experimental and clinical studies.

An Orphan Drug

In 1991, several batches of the botulinum toxin-A and all research findings concerning this "orphan drug" were bought by Allergan Inc., Irvine, who, as new parents, gave the substance the name Botox®.[13] Two years later, Porton Products Ltd, a British company, launched a slightly different formulation, and named it DYSPORT® (Ipsen Inc., Rockford, IL 61125-1266.), derived from the word dystonia.

In the recent past, various subtypes have been found, such as type A, B, C, D, E, F, and G, and a variety of different products containing botulinum toxin-A strains are on the market with numerous indications for the medical use of this drug. Derived from food poisoning 200 or more years ago, the toxin has made its way and, for many reasons, it is probably the most amazing substance that has been developed as a revolutionary pharmaceutical in the past decades.

Learning points:

- In 1821, after receiving a grant from the government of Stuttgart, Kerner started his study on sausage poisoning and observed the action of the toxin to be on the peripheral sympathetic and parasympathetic nerves and its signal interruption, without any sensory disturbances.
- In 1897, different serological subtypes were discovered after subsequent investigations.
- In the 1920s, botulinum toxin was used as a biological weapon by the US Academy of Sciences at the beginning of World War II.
- The first botulinum toxin for human use was produced in 1946 by Edward Schantz, a scientist at Fort Detrick.
- In 1978, Scott received permission from the FDA to conduct a pilot study on human volunteers for the treatment of strabismus
- Later on, in 1989, the FDA approved the use of botulinum toxin-A for hemi-facial spasms, strabismus and blepharospasms.
- The first report on botulinum toxin in cosmetic procedures was published in 1996 by Carruthers.

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Chapter 3

Pharmacology: Understanding the Drug

Monica Patil, Kumar Nilesh

Neuromuscular transmission

To know the mechanism of action of botulinum toxin, it is important to understand the steps involved in cholinergic neurotransmission, at the neuromuscular junction. Cholinergic neurotransmission involves six basic steps: the synthesis, storage, release, binding, degradation, and recycling of acetylcholine[1] (Chart 3A).

At the first step, choline is transported from the extracellular fluid into the presynaptic neuron's cytoplasm. This is brought by a carrier system that also co-transports sodium. In the cytoplasm of the neuron, choline reacts enzymatically with acetyl coenzyme A to form acetylcholine. The acetylcholine is aggregated into the synaptic vesicles, where it is stored in granules. When an impulse is initiated and transmitted across the neuron, the action potential ultimately arrives at the nerve ending (at the neuromuscular junction). The voltage-sensitive calcium channels in the presynaptic membrane open up, causing an increase in the intracellular calcium concentration. Elevated calcium levels promote the docking and subsequent fusion of the synaptic vesicles containing acetylcholine with the cell membrane. This is conducted via a complex mechanism involving protein isoforms, ultimately resulting in the release of acetylcholine. Acetylcholine subsequently diffuses across the synaptic junction and binds at the postsynaptic nicotinic receptors on the muscle fiber. This binding activates a second messenger system that results in the contraction of the muscle. Following this, acetylcholine is rapidly broken down into choline and acetate by the enzyme, acetylcholinesterase. Choline can be recycled by the high-affinity transport system that pulls the molecule back into the neuron.[2]

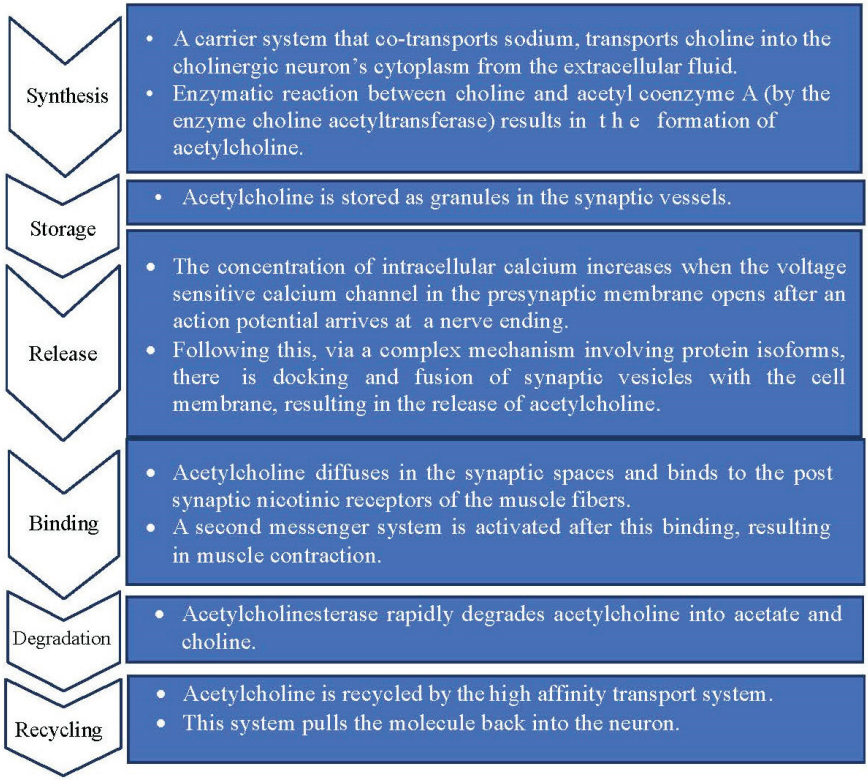

Chart 3A: Flowchart of neuromuscular transmission

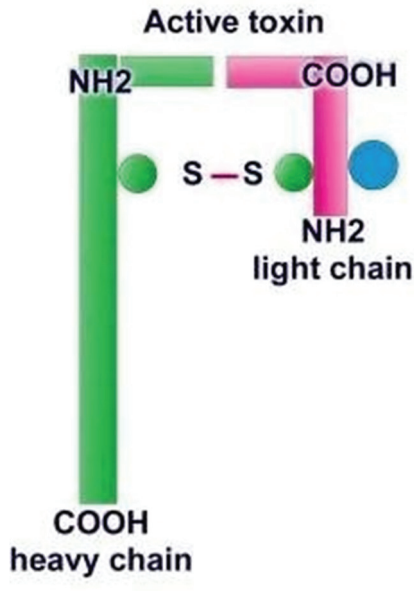

Figure 3A: Line-diagram showing structure of botulinum toxin.

Botulinum toxin structure

Botulinum neurotoxin exist as inactive polypeptides of 150 kilodalton (kd). These are split by trypsin like bacterial protease and generate the active double-chain form of the toxin. The proportion of single to double-chain varies according to the serotype of the toxin and whether the bacterial strain expresses the appropriate protease or not.[3] The 100-kd heavy (H) chain and the 50-kd light (L) chain are linked together by heat labile di-sulfide bonds and noncovalent forces.[4] Both the H and the L chains have carboxy (COOH) and amino-terminal (NH2) terminals (Figure 3A). The H and L chains dissociate with heat and boiling, which inactivates the toxin (because neurotoxicity requires both H and L chains).[5]

Molecular actions of botulinum toxin

All the serotypes of botulinum toxin act on the peripheral nervous system. It acts at the neuromuscular junction by inhibiting the release of acetylcholine from its presynaptic terminal. In very large doses, the toxin may show autonomic effects by binding to the

nerve terminals at the autonomic cholinergic ganglia. However, at therapeutic doses, the toxin is very unlikely to be associated with any significant adverse autonomic reactions[5] (Figure 3B). The neurotoxicity of botulinum toxin involves three steps:

1. Binding
2. Internalization
3. Neuromuscular blockage

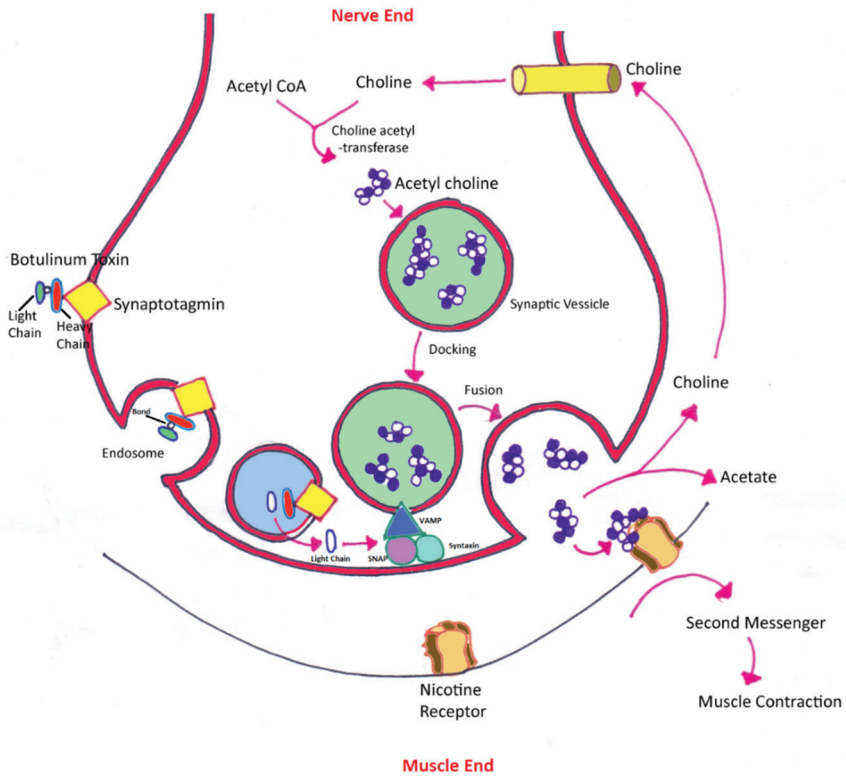

Figure 3B: Line-diagram showing acetyl choline release at the synaptic junction and mechanism of action of botulinum toxin

1. Binding

The first step involves the irreversible binding of the botulinum toxin to the presynaptic receptor. The binding happens with the help of the carboxy-terminal of botulinum toxin's heavy chain.[6-8] The exact binding site for the toxin has not been definitely identified. Previous studies suggested that distinct receptors exist for different botulinum toxin serotypes.[6] However, this view has been contradicted by the isolation of the synaptic vesicle protein, synaptotagmin. Synaptotagmin demonstrates a binding ability with botulinum toxin A, B, and E.[9]

2. Internalization

The second step involves the internalization of the botulinum neurotoxin. This occurs through receptor-mediated endocytosis. This process of internalization is partially dependent on the nerve stimulation. After internalization, the toxin molecule is present in the cytoplasmic endosomes. Subsequently, there is cleavage of the di-sulfide bond resulting in the separation of the heavy and light chains. The exact mechanism leading to this cleavage is unknown. There is a translocation of the L-chain from the endosome into the neuronal cytoplasm.[10]

3. Neuromuscular blockage

Within the nerve cytoplasm at the synaptic end, various large protein isoforms are present. These mainly include: syntaxin, vesicle associated membrane protein (VAMP) and synaptosomal associated protein (SNAP-25). These proteins form a complex platform which is necessary for the docking, fusion, and release of acetylcholine containing synaptic vesicles through the cell membrane.[11] Thus, the release of acetylcholine brings about the impulse transmission and muscle contraction.

The third and final step in the action of botulinum toxin involves neuromuscular blockage. The L-chain of botulinum toxin contains a highly specific zinc-endopeptidase at its amino-terminal which cleaves the protein complex with its proteolytic activity. Disintegration of the protein complex prevents the fusion and release of acetylcholine from the synaptic vesicles.[5] This results in a blockage of the impulse transmission and, subsequently, the muscle contraction is prevented.

Drug and disease interaction with botulinum toxin

Various drugs act on the neuromuscular junction and interfere with the action of botulinum toxin.

- **Aminoglycoside antibiotics** enhance the action of botulinum toxin. Aminoglycosides, such as kanamycin, gentamycin, and streptomycin in large doses can avert the release of acetylcholine from the nerve endings, producing a clinical syndrome similar to botulism. This effect is believed to be related to calcium channel blockage. Symptoms rapidly subside with the elimination of the offending drug from the body.

- **Aminoquinolines** act as antagonists to the effects of botulinum toxin by acting intracellularly, inhibiting the toxins lysosomal processing or acting on the cell membrane by inhibiting the toxin binding.

- **Cyclosporine** has also reportedly been shown to bring about neuromuscular blockage due to some unknown mechanism that is characterized by muscle weakness and ventilatory failure. However, the results may be due to the anti-inflammatory or immunosuppressive effects of cyclosporine on muscle or blockage of the presynaptic calcium channels.

- **D-Penicillamine**, in immunologically predisposed individuals, may trigger the formation of acetylcholine receptor antibodies, resulting in symptoms of myasthenia gravis. This can be seen in a small percentage of patients with rheumatoid arthritis. The symptoms and the antibodies diminish within a few months after drug cessation.

- In patients with **neuromuscular transmission disorders**, the use of botulinum toxin is contraindicated. In Lambert-Eaton myasthenic syndrome (LEMS), antibodies that are directed against the tumor antigens cross-react with the voltage-gated calcium channels that are involved in acetylcholine release. This leads to a disturbance of neuromuscular transmission. The antibody-induced internalization and acetylcholine receptor's degradation causes weakness in myasthenia gravis.

Assays and pharmacological actions

Muscle assay

There are several assays that explain the pharmacological action of botulinum toxin. The multistep hypothesis of botulinum toxin has been established by the mouse phrenic nerve diaphragm model.[12] Histologic analysis and toxin radio-labelling coupled together described the relationship among the toxins, motor end plates, and receptor sites. It demonstrated that the toxin binds more rapidly to the nerves of actively contracting muscles.[13]

The mouse hypoglossal nerve assay revealed that, unlike the toxicity caused to the neuron cell body by retrograde transport due to the doxorubicin, botulinum toxin does not induce motor-neuron death but causes a chemical denervation of the neuromuscular junction.[14, 15]

The denervation is reversible and was demonstrated by studies on muscle fibers from human blepharospasms. Acetylcholine esterase stain was used to assess the denervation of striated muscles after injecting botulinum toxin and it was observed that denervation is accompanied by spreading of the acetylcholine esterase activity to cover most of the exposed sarcolemma. After 4-5 months, the distribution of acetylcholine esterase activity returned back to its normal pattern.[16] Neurogenesis, with the formation of axonal sprouts within ten days and new motor end plates aids in recovery from denervation and the nerve terminals and muscle motor end plates are therefore reconnected.[17]

The muscle atrophy is also reversible and was demonstrated by the rabbit longissimus dorsi muscle assay. Within two weeks of injection with the toxin, the muscle atrophy was seen which continued for about four weeks before reversing.[18] Similarly, patients with orbicularis oculi muscles of blepharospasm treated with botulinum toxin showed reversible denervation atrophy.[16] About 3-6 months were required for clinical functional recovery of the muscles by which time the muscle returned to about 70-80% of its original bulk.[5] However, sprouting and remodeling may continue for up to three years.[19]

Bioassay

The mouse biologic assay is currently the only accepted quantitative method for the detection of Clostridium toxins in culture, serum, and food samples and for antitoxin standardization.[20, 21] It is also the most specific and sensitive measurement of botulinum toxin activity.

One mouse unit (MU) is defined as the median intraperitoneal dose required to kill 50% of a batch of 18 to 20 g of female Swiss-Webster mice (LD50) in over three to four days.[22-24] The original assay which was measured in monkeys, was found to be less narrow compared to the lethal dose effects in mice.[25] The LD50 of botulinum toxin-A for humans, extrapolated from the studies in monkeys, is estimated to be about 40 MU/kg.[26] For a normal human of 70 kg weight, the LD50 is found to be in the range of 2500–3000 MU. The presence of possible species variability in the botulinum toxin sensitivity prevents an accurate calculation of the toxic dose for humans.[5] Nevertheless, the safety margin for a therapeutic dose is quite wide. For example, in the treatment of glabellar frown lines, the required average number of units is about 30 units. However, the most significant drawback of the mouse bioassay is that it does not provide an accurate characterization of botulinum toxin potency in human subjects.[27] Clinical potency of the toxin in humans is also dependent on the targeted muscle, the toxin dose, and the volume.

Immunoassays

Compared to the mouse bioassay, assays that use monoclonal antibodies, like immunodiffusion and the hemagglutination assay are still not sensitive enough. Radio-immunoassay is also inapplicable for the sample's routine testing because of the requirement to radiolabel the toxin and it also requires a suitable radiologic facility.

However, the enzyme-linked immunoassay (ELISA) shows the greatest potential as a replacement for the bioassay, as the standard technique using polyclonal antibodies is reasonably rapid, highly specific, and can be applied to the testing of a large number of specimens.[20] The redox cycle amplification system, or an enzyme-linked coagulation amplification system, can further improve the sensitivity of the ELISA.[28] Nevertheless, the inability of all ELISA based assays to distinguish between active and inactive

forms of toxin remains the major disadvantage. A specific assay based on botulinum toxin endopeptidase activity that directly measures the biologic activity of the toxin is being investigated.[29-30]

Yet, the mouse bioassay may not be totally replaced by these in vitro assays, as they do not provide a measurement of other parameters that contribute to the overall toxicity and therapeutic potency, making the mouse bioassay the gold standard for toxin detection and standardization.

Immunogenicity

The toxin's immunological properties can cause stimulation of antibody production, that can potentially lead to ineffective treatments. The minimum dosage and injection schedule required to induce antibody formation are unknown. However, it has been shown that immunogenicity depends on the dose per session, the cumulative dose and the frequency of administration.

Biglan et al. published a study which revealed that there was an absence of antibody formation in patients who received less than 50 IU per session.[31] Gonnering published a study in which he reported antibody response in the patients of syndromic facial spasms who received doses in the range of 150-300 IU per session, but which was not seen in patients who received doses up to 52.5 IU for a period of three years.[32] Jankovic and Schwartz tested antibody production in cervical and oromandibular patients.[33] A statistically significant difference was seen in patients who received a cumulative dose of 1709 IU with antibodies and patients who received a cumulative dose of 1066 IU without antibodies. In a study on patients with torticollis, who were treated with doses ranging from 150-300 IU, these patients demonstrated a prevalence of neutralizing antibody in 4.3% of cases.[34] It was also noted that patients who were resistant to botulinum toxin required more frequent and booster injections, two to three weeks post-treatment. However, in patients with blepharospasm or patients treated for dermatologic problems, antibody formation has not been reported to date.

The mouse neutralization assay is the most widely used test. However, this test is time consuming and expensive. More rapid immunoassays have been developed to detect the antibodies. However, their lower specificity and lack of correlation between

clinical resistance and detected antibodies remains the major drawback. The combination of these two types of tests may give the most sensitive and specific results.

Using the smallest effective dose possible, treatment intervals of at least three months and avoidance of booster injections may minimize antibody resistance. Patients with botulinum toxin-A resistance may respond to botulinum toxin-B.

Adverse effects

The uncommon minor adverse effects of botulinum toxin injection are: hematoma, bruising, itching and pain at the injection site. All of these effects range from mild to moderate in intensity and recover after some time. Improper muscle injection can also result in transient ptosis, lip drooping, ectropion, and diplopia. Severe anaphylaxis, attributable to botulinum, have been reported after almost a decade of therapeutic application.[36] Local changes in muscle fiber size and electromyographic abnormalities may be the long-term complications of botulinum toxin. However, they are mild and do not have any clinical significance. There is no central nervous system effect of botulinum toxin, as it does not cross the blood brain barrier.[37]

Learning points:
▪ Cholinergic neurotransmission involves six steps: synthesis, storage, release, binding, degradation, and recycling of acetylcholine.
▪ The mechanism of neuromuscular transmission of botulinum toxin involves three steps; binding, internalization, and neuromuscular blockage.
▪ Botulinum toxin acts at the neuromuscular junction by inhibiting the release of acetylcholine from its presynaptic terminal.
▪ Aminoglycoside antibiotics enhance the action of botulinum toxin, whereas aminoquinolines act as antagonists to the effects of botulinum toxin.
▪ There are several assays that explain the pharmacological action of botulinum toxin including: muscle assay, bioassay, and immunoassay.

- Immunogenicity of botulinum toxin depends on the dose per session, the cumulative dose and the frequency of administration. However, using the smallest possible effective dose, treatment intervals of at least three months and avoidance of booster injections can minimize antibody resistance.

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Chapter 4

Preparations: Commercial Availability

Kumar Nilesh, Monica Patil, Aaditee Vande

Commercially, only two botulinum toxin-A preparations are available: Botox® (Allergan, Inc., Irvine, Calif.) and Dysport® (Speywood Pharmaceuticals, Maidenhead, England). Botox is three to five times more potent than Dysport.[1] Commercially, serotype A is the only FDA approved form of botulinum toxin for clinical use.

Botox® is a sterile, vacuum-dried form of purified botulinum toxin-A. It is produced from a culture of Clostridium botulinum that is grown in a medium containing yeast extract and N-Z amine. It is then isolated by a series of acid precipitations from the culture to a crystalline complex that consists of the active high molecular toxin protein and an associated hemagglutinin protein. The crystalline complex is again dissolved in the solution of saline and albumin for stability and is sterile-filtered, then vacuum-dried. In the Schantz preparation, 1 IU of the crystalline protein complex weighs about 0.043 ng.[2] The amount of chromatographically purified botulinum-A toxin is approximately 0.006 ng.[3] Each vial of Botox® contains 100 IU of botulinum toxin-A, human albumin (0.5mg) and a sterile, vacuum-dried form of sodium chloride (0.9mg) without preservatives. Reconstituted for clinical use, the vials are stored in a freezer. Non-preserved saline is recommended as a diluent, as preserved saline may alter the dose response during reconstitution. Also, excessive shaking and bubbling should be avoided as it may inactivate the toxin. The product should be stored at 2°C to 8°C in the refrigerator after reconstitution.

The Dysport® preparation is different from Botox® in terms of its biological activities, chemical properties, and weight. Unlike Botox® it is produced by column-based purification and is supplied in 300 IU vials, and may be stored at room temperature. The Botox unit is three to five times more potent than the Dysport unit.[1] Comparison between two formulations is summarized in Table and Figure 4A.

Table 4A: Comparision between two formulations of botulinum toxin	
Botox® (onabotulinumtoxinA)	Dysport™ (abobotulinumtoxinA)
FDA approved for cosmetic use in 2002 (but its use was popularized well before)	FDA approved in 2009 (but has been widely used in Europe since the early nineties)
Comes in 100-unit vials	Comes in 300-unit vials
One important point to note is that dilution is different between the two products. One unit of Botox® does NOT equal one unit of Dysport™. Rather, one unit of Botox® is equal to about 2 to 3 units (2.5) of Dysport™.	
Botox® is vacuum dried in NaCl and albumin	Dysport® is freeze-dried in lactose and albumin
Given the compounding with lactose, there are trace amounts of cow milk protein in Dysport™. Hence, care must be taken in patients with a cow milk allergy. In such instances, one should consider Botox™ over Dysport™.	
It has been suggested that Dysport ™ has a quicker onset of action. Results being reportedly seen within 24 hours of its use (compared to two to three days for Botox™)	
Does one last longer than the other? Not definitively known	
Does Dysport have a greater dispersion area? Not definitively known	
Price comparison A vial of Botox® is more expensive than a vial of Dysport™ .	

Figure 4A: Commercially available formulations of botulinum toxin A: Botox® (a) and Dysport® (b).

Storage

The biological potency of Botox® may be affected after storage. The current FDA-approved product labelling recommends that it should be used within four hours of reconstitution with normal saline.[4] This makes the use of Botox® somewhat difficult in clinical settings.

Several studies have investigated the relationship between the storage and potency of botulinum toxin. One of the studies using the mouse bioassay showed no loss of activity six hours after reconstitution at room temperature.[4] However, when left for 12 hours, a loss of up to 44% activity was observed. Re-freezing the toxin after reconstitution was reported to cause approximately 70% loss of bioactivity after one to two weeks.[5] In a human extensor digitorum brevis model, Sloop, Cole, and Escutin showed no loss of potency in the reconstituted toxin after refrigeration or refreezing for 2 weeks.[6] Using the time-stored diluted Botox®, Lowe[7] observed a 50% decrease in the efficacy of Botox to reduce hyper-functional facial lines after one week. Another study demonstrated that toxin at 10 IU/ml reconstituted 30 days before injection produced paralysis of the facial muscle tone equivalent to that of freshly mixed toxin.[8] All studies used unpreserved normal saline for reconstitution. Although there are no standardized guidelines for storage, most

clinicians do not refrigerate the toxin for more than one week. Refrigeration for less than 24 hours is optimal, and refreezing is discouraged.[9]

Dose and Response Relationship

The effect of Botulinum toxin varies according to the location, concentration, and volume of solution injected. The concentration of the solution used for cosmetic indications varies from 10 IU/ml to 100 IU/ml and the volume in each location ranges from 0.025 to 1.0ml per site.[10] According to the size of the muscle to be treated, the volume and concentration of botulinum toxin is increased. Dosing still remains arbitrary and is based on the physician's experience. The art of using botulinum toxin comes from choosing the desired weakening of muscle contraction without causing unwanted muscle paralysis. The most effective dose at the smallest volume should be used in order to achieve maximal dose response and minimize side effects. A small volume and high dose tends to localize the toxin and contains a biological effect of muscle paralysis. A large volume and small dose weakens the muscle and produces a smoothening effect with a risk of toxin spreading to the adjacent muscles.

Table 4B: Contraindications for use of botulinum toxin

▪ Subjects with known allergy to botulinum toxin or albumin
▪ Patients with amyotrophic lateral sclerosis, motor neuropathy, myasthenia gravis, or Lambert-Eaton syndrome
▪ Pregnant women and those planning a pregnancy
▪ Breast feeding women
▪ Patients on medications, including: aminoglycosides, anticholinesterases, and other agents interfering with neuromuscular transmission.

The toxin can be safely administered in patients. The common side effects of botulinum toxin include: muscle weakness, pain, swelling, redness, and itchiness at the site of injection. These complications are usually mild to moderate in severity and transient. The undesirable muscle weakness recovers as the effect of the toxin starts to diminish. However, in certain conditions its use is relatively or strictly contraindicated and is summarized in Table 4B.

Learning points:
▪ Two botulinum toxin-A preparations are available commercially: Botox® (Allergan, Inc, Irvine, Calif.) and Dysport® (Speywood Pharmaceuticals, Maidenhead, England).
▪ Botox is three to five times more potent than Dysport.
▪ Non-preserved saline is recommended as a diluent, as preserved saline may alter the dose response during reconstitution.
▪ Refrigeration of the toxin after reconstitution for less than 24 hours is optimal, and refreezing is not recommended.
▪ Dosing of botulinum toxin still remains arbitrary and is based on the physician's experience and varies according to the location, concentration and volume of solution injected.

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Chapter 5.1

Cosmetic Applications of Botulinum Toxin for the Management of Glabellar Lines/Rhytids

Kumar Nilesh, Monica Patil, Eesha Pisal

Rhytids are facial lines that are typically perpendicular to the orientation of muscle fibers. Glabella is the skin between the two eyebrows and above the nose. Depending on the face shape, skin tightness, genetics, and on how frequently one makes certain facial expressions, wrinkles begin to develop between the eyebrows and are known as frown lines or glabellar rhytids. In 1987, Dr. Jean Carruthers observed that patients treated with botulinum toxin for blepharospasm showed improvement in the glabellar rhytids. Since then, botulinum toxin has evolved as one of the most popular treatment options for glabellar rhytids. Over the last two decades, the field of cosmetic dermatology has been revolutionized by the use of botulinum toxin.

Anatomy

It is essential to have knowledge of the underlying muscles that are to be treated by botulinum toxin therapy, so as to achieve precision of treatment, improve the clinical outcome and avoid undesirable complications. The glabellar complex consists of the following muscles:

- Corrugator supercilia muscle
- Procerus muscle
- Frontalis muscle
- Orbicularis oculi muscle

Surgical anatomy of these muscles is described in Chart 5.1A and Figure 5.1A.

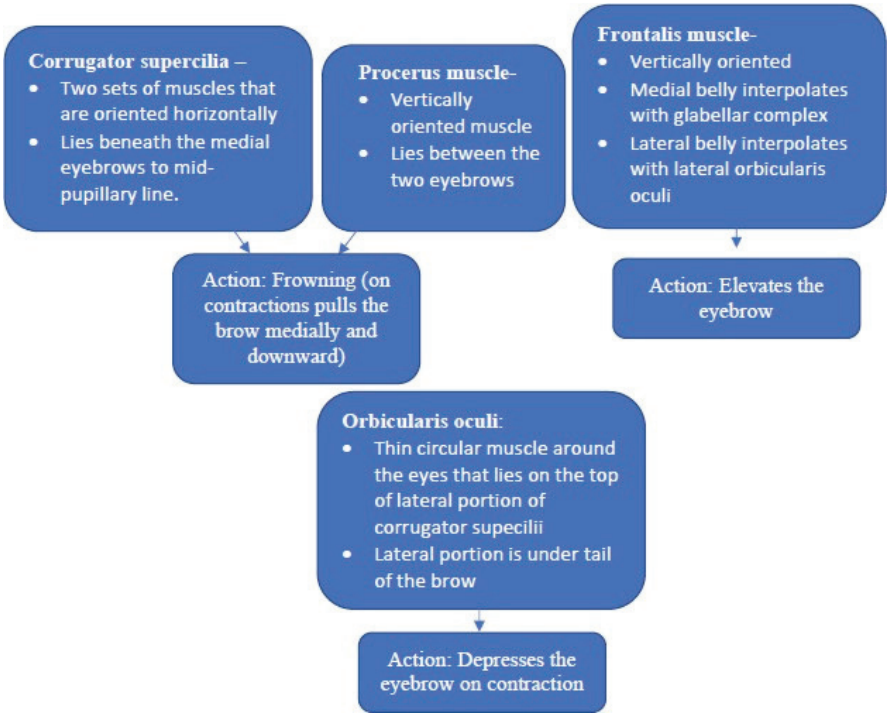

Chart 5.1A: flowchart describing muscles of glabellar complex

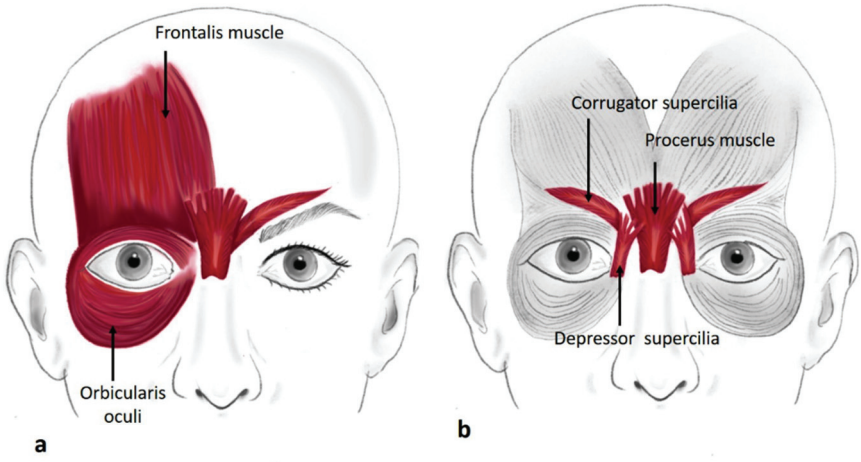

Figure 5.1A: Diagrammatic representation of the anatomy of glabellar complex

Injection technique:

A 1ml insulin syringe and a 30 to 32-gauge needle are commonly used for injection.

There are typically 5 injection sites in the region of the glabella:

1) Each medial corrugator
2) Each lateral corrugator (at the mid-pupillary line 1cm above the orbital rim)
3) Single injection at the procerus.

In patients with long and strong corrugator muscles, an additional site is selected for injection midway between the lateral and medial corrugator sites of injection.

The steps in injection of botulinum toxin:

1. The operator should stand in the front, facing the patient. The patient is asked to look straight forward, at midline point on the operator's face. The patient is then asked to frown. This helps in visualizing the corrugator supercilia and procerus muscle as they contract, and to visualize the mid pupillary

line with exact symmetry.

2. Injection sites are marked with a marker (Figure 5.1B, C).
3. The thumb of the non-injecting hand is kept on the supraorbital rim for precision. The patient is asked to contract while the operator holds the corrugator muscle between the thumb and the forefinger. This allows a proper isolation of the muscle, preventing accidental injections below the rim. This helps to eliminate the risk of ptosis post-operatively.
4. The patient should be instructed not to contract during actual injection.
5. Various methods can be used to control pain during the botulinum toxin injection, and include:
   a. Intrafollicular orifice injection
   b. Pre-injection topical anesthetic application
   c. Ice application
   d. Using smaller gauge needles
   e. Diluting using preservative containing sodium chloride solution.

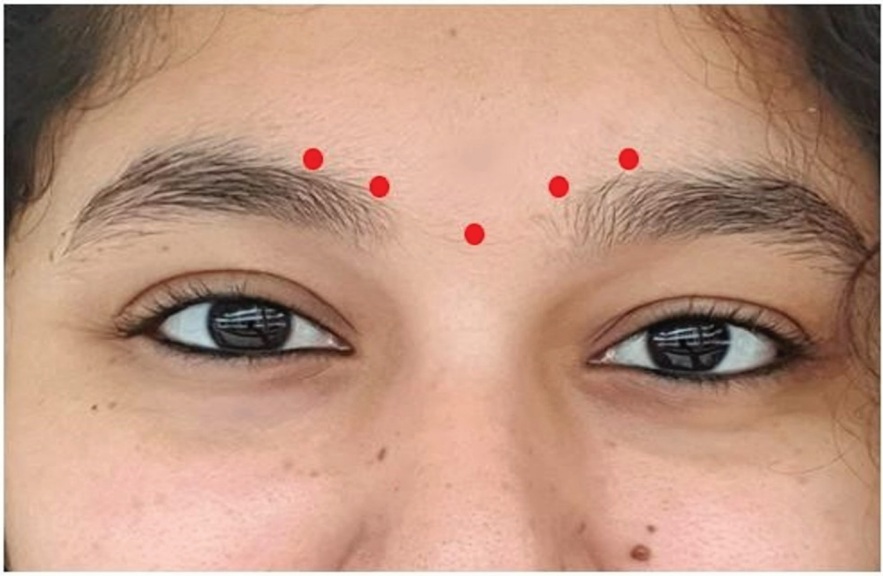

Figure 5.1B: Injection sites for correction of glabellar rhytids

Figure 5.1C: Injection technique for glabellar rhytids

Dosage:

1. BOTOX®

Standard dilution: 100 IU of Botox® vial is diluted with 2.5 ml of 0.9% normal saline. This gives four units of botulinum toxin in a single injection of 0.1ml.

- *Women:* In glabellar complex, a total of 20-24 IU of Botox® is injected via five injection points
- *Men:* Depending upon the strength of the muscle contraction of the glabellar complex, 20-40 IU or more may be injected.

A study conducted in 2005 by Carruthers et al. on 80 men, who randomly received 20, 40, 60, and 80 IU of botulinum toxin-A, showed that the 40, 60, and 80 IU doses showed more effective results in reducing glabellar lines than the lower dose of 20 IU.[1] Onset of the response of the toxin is typically seen in 1-14 days and the results last for about three to four months. Dailey and co-workers in their study found that a 20 IU injection of Botox® in

glabellar complex, injected at an interval of every four months for 20 months, progressively eliminates glabellar rhytids for about 6 months after the last treatment.[2] The result of botulinum toxin injection in the management of glabellar rhytids is presented in Figure 5.1D.

2. DYSPORT®:

Standard dilution: 300 IU of Dysport® vial is diluted in 2.5 ml or 1.5 ml of 0.9% sodium chloride (without preservatives). This gives 10 IU solution per 0.08 ml when diluted in 2.5 ml of sodium chloride and 10 IU per 0.05 ml when diluted with 1.5 ml sodium chloride.

Monheit et al. conducted a randomized, doubled-blinded placebo-controlled study of Dysport® to determine its optimal dose in the correction of glabellar rhytids. Participants were injected with 20, 50, or 75 IU of Dysport® and were followed up for an interval of 7, 30, 60, 90, and 120 days. Significant results were seen and an optimal dose of 50 IU was determined. In a competitive study between Dysport® and Botox®, relapse at week 16 was 40% in the Dysport® group, compared to 23% in the Botox® group. The onset of action was found to be one to two days earlier in Dysport®. However, the efficacy of both the products was found to be similar.[3]

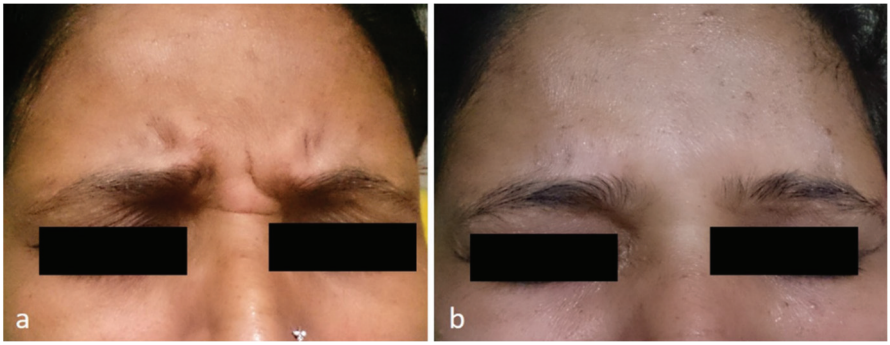

Figure 5.1D: Preoperative (a) and postoperative (b) images showing treatment of glabella region using botulinum toxin.

Complications

Pain at injection site, edema, bruising, headache, eyebrow ptosis, and upper eyelid ptosis are the most common adverse effects of

using botulinum toxin in the glabellar region. Lid ptosis can manifest as an early complication within 48 hours and as late as a week after injection and can last for weeks. It typically resolves within two to six weeks.

Alpha adrenergic agonist ophthalmic eye drops may be used to correct the eyelid ptosis which may result as a complication of botulinum toxin injection. The Müller muscle is stimulated as an effect of these drops that helps in elevating the ptotic eyelid. The standard dose of these drops is two drops, for two to three times a day, until the ptosis resolves.

Learning points:
▪ The cosmetic use of botulinum toxin for glabellar rhytids was approved by the FDA in 2002.
▪ Glabellar complex includes: corrugator supercillia and procerus muscles
▪ FDA approved botulinum toxins used in the glabellar complex are Botox and Dysport, at doses of 20 units and 50 units respectively. To obtain optimal correction, variations of doses may also be required. Men may require a higher range of doses compared to women.
▪ Pain at injection site, edema, bruising, headache, eyebrow ptosis, and upper eyelid ptosis are the possible, but reversible, complications of use of botulinum toxin in the glabellar region.

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Chapter 5.2

Cosmetic Applications of Botulinum Toxin in Eyebrow Lift

Arun Kumar Panda, Kumar Nilesh, Monica Patil

Eyebrow height and shape are one of the important determining factors of beauty and youthfulness. Brow height and contour can be subtly enhanced by botulinum toxin, thereby improving the patient's attractiveness.

After the first report was published in 1992 on the treatment of glabellar frown lines with botulinum toxin, several clinicians started noticing a slight brow elevation on treating the glabella. Frankel and Kamer proposed that, as the medial shape and height of the eyebrow was because of the interplay between the frontalis muscle that lifts the eyebrow and the depressor muscles, selective injection of the depressor muscle with botulinum toxin would result in the elevation of the medial brow. To test this, Frankel and Kamer injected 20 IU of botulinum toxin-A in the procerus and the corrugator supercilia muscles in 30 patients and observed that in around 32% of the patients, the eyebrow height at the mid-pupillary and mid-canthal region was raised.[1]

In 2007, Alastair and Jean Carruthers published a study on a dose-ranging, randomized controlled trial that assessed the eyebrow elevation after a glabellar injection with botulinum toxin. They followed the standard glabellar injection pattern with seven sites in their study. These seven sites were treated with 10, 20, 30, or 40 IU of botulinum toxin and the brow height was then assessed retrospectively using photographs before treatment and then after, every two weeks for around 20 weeks. Significant brow height elevation was noted at all sites injected with 20, 30, and 40 IU. There was dramatic elevation of the lateral brow within two weeks in patients treated with more than 20 IU, followed by gradual elevation of the eyebrow, reaching its peak at the 12th week.[2] However, it was noted that the effect of botulinum toxin in brow elevation had limited

effect on the weakening of the brow depressor muscles. The most lateral injections in the reported trials were made above the mid pupillary line and the earliest and most dramatic effect was seen at the lateral brow. This showed that the eyebrow elevation may be more likely to be because of the weakening of the infero-medial frontalis muscle. This resulted in a compensatory increase in the resting tone of the remaining lateral portion of the muscle.

Eyebrows and attractiveness

Eyebrows constitute the primary determinants of facial attractiveness and play an important role in conveying emotions. Age, gender, ethnicity, culture and current fashion trends influence the ideal eyebrows. Uni-brow (eyebrows extending across the midline) was considered ideal in ancient Greece. However, this style of eyebrow is not considered ideal now.

In 1974, Westmore proposed the modern concept of the ideal contour of the female eyebrow[3] (Figure 5.2A). This concept is best applied on an oval face and is considered a good starting point, as there is no clear definition of an ideal eyebrow which can be applied on all types of face.

The ideal apex of the eyebrow, as suggested by many authors, is more lateral to the lateral limbus of the eye, than what was originally suggested by Westmore. Too medial an apex of the eyebrow creates an over-elevated and surprised appearance. Variations to Westmore's ideal eyebrow have been suggested according to the different face shapes and intercanthal distance (Figure 5.2A).

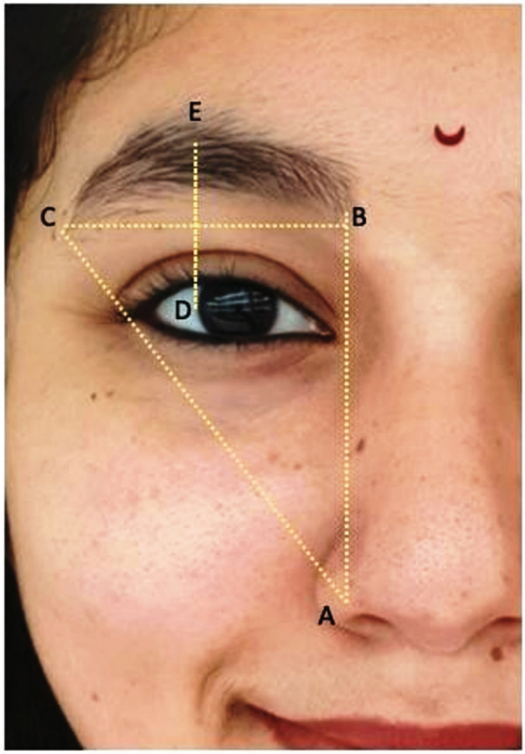

Figure 5.2A: Ideal contour of the female eyebrow; Medial aspect should begin on a vertical plane with the ala of the nose. The apex should be above the lateral limbus and the lateral aspect should end on a horizontal plane with the medial eyebrow at a point where an oblique line can be drawn from the ala of the nose through the lateral canthus of the eye.

Matros et al. stated that as a female's age increases, the resting medial height of the eyebrow is raised.[4] In younger age, women tend to have more lateral elevation of the eyebrow. Hence, if the eyebrow is completely raised, the cosmetic results are disappointing. The ideal eyebrow in men is placed lower, compared to the female's eyebrows, thus shaping more horizontally with minimal arching. The ideal eyebrow shape also varies depending on the type of shape of individual's face *(Figure 5.2B).*

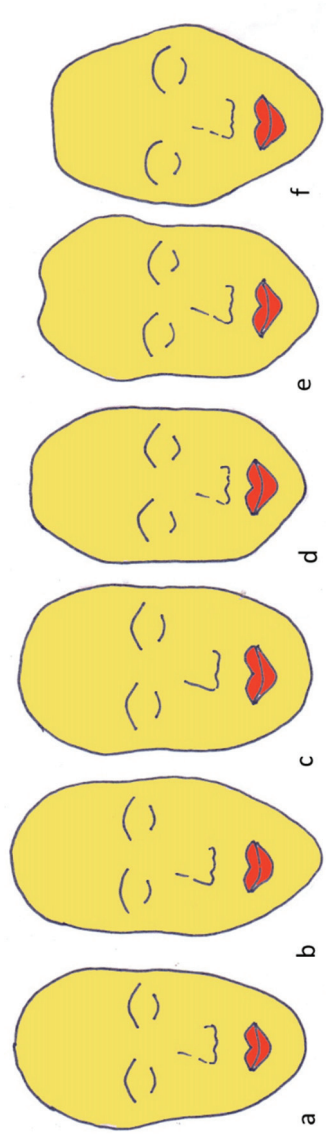

Figure 5.2B: Various types of face shapes; oval (a), long (b), round (c), square (d), heart shaped (e), and diamond shaped (f).

Table 5.2A: Face types and ideal eyebrow shape	
Face Type	**Desired eyebrow shape**
Oval face	Ideal
Long face	To make the face appear more oval, eyebrows should be more horizontal
Round face	For the face to appear more oval, eyebrow should go up. High arched eyebrows with lateral apex are ideal.
Square face	Angled eyebrows balance the strong jaw line. The apex should be above the square of the jaw if possible.
Heart shaped face	Rounded brows are ideal as they add curves, soften the appearance and emphasize the shape of the face.
Diamond shaped face	The angular face can be softened by round eyebrows.

Anatomy

The opposing forces of the frontalis muscle (eyebrow elevator) and the eyebrow depressors (procerus, corrugators, depressor supercilia, and orbicularis oculi) determine the height and the shape of the eyebrow (Figure 5.2C and Table 5.2B).

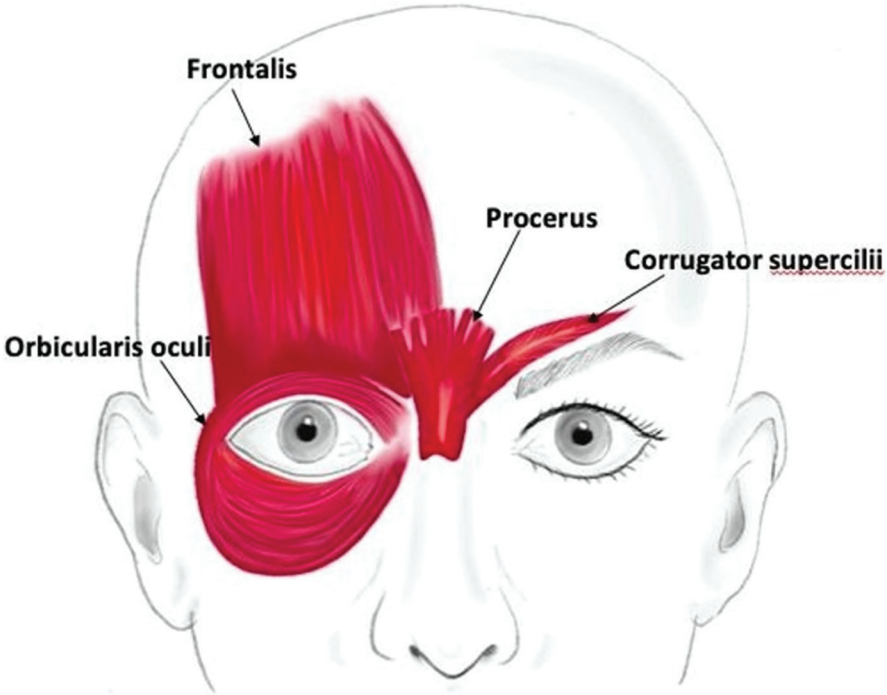

Figure 5.2C: Diagrammatic representation of muscles involved in eyebrow lift

Table 5.2B: Eyebrow elevator and depressor muscles

Elevator muscle (frontalis)	Depressor muscle
Origin: Galea aponeurosis **Insertion:** it does not have any bony insertions. **It continues** • Medially with procerus muscle • Centrally attaches to corrugator supercilia • Laterally with orbicularis oculi (these muscles are in turn attached to the skin of the eyebrow)	**Medial**: Procerus, corrugator supercilia, medial portion of orbicularis oculi and depressor supercilia **Lateral**: lateral portion of orbicularis oculi.

Corrugator supercilia is a pyramid shaped, small (around 2-3 cm), but strong muscle that arises at the glabellar prominence, about 7 mm from the midline and about 11 mm above the orbital margin. It lies beneath the frontalis muscle, passing laterally upwards between the palpebral and orbital fibers of the orbicularis oculi and inserts at the mid-pupillary level in the skin of the eyebrow. The medial eyebrow is pulled downwards into a frown with the contraction of the corrugator supercilia. At the center of the medial brow, corrugator supercilia are the thickest.

Procerus muscle is a vertically oriented muscle that lies between the two eyebrows. Along with the corrugator supercilia it helps in frowning.

Orbicularis oculi is a sphincter shaped muscle that is responsible for eyelid closure. It forms a ring around the eye extending superiorly and inferiorly after arising from the medial orbit. The outer portion of this muscle is thick, and the contraction of this outer ring closes the eyelid tightly and pulls the eyebrow downward.

Frontalis muscle is a vertically oriented muscle with its medial belly interpolated with the glabellar complex and its lateral belly interpolated with the lateral orbicularis oculi muscle. The action of the frontalis muscle is to elevate the eyebrow.

Technique of injection of botulinum toxin:

The following preoperative evaluation should be done before botulinum toxin injection for eyebrow lift:

1. Resting and dynamic evaluation of the brows should be done at the first appointment.

2. Palpation of the corrugator supercilia and procerus muscles should be done to find the target belly and assessment of the initial dose depending on the glabellar muscle's strength (measured by the range and blanching of the frowned skin) should be done.

3. Pretreatment photographs should be taken and any eyebrow asymmetry observed should be pointed out to the patient.

4. Treatment goals should be determined after considering the patient's age, face shape, and asymmetry.

Injection technique:

1. Five to 7 injection sites are typically considered for the standard glabellar injection (Figure 5.2D).

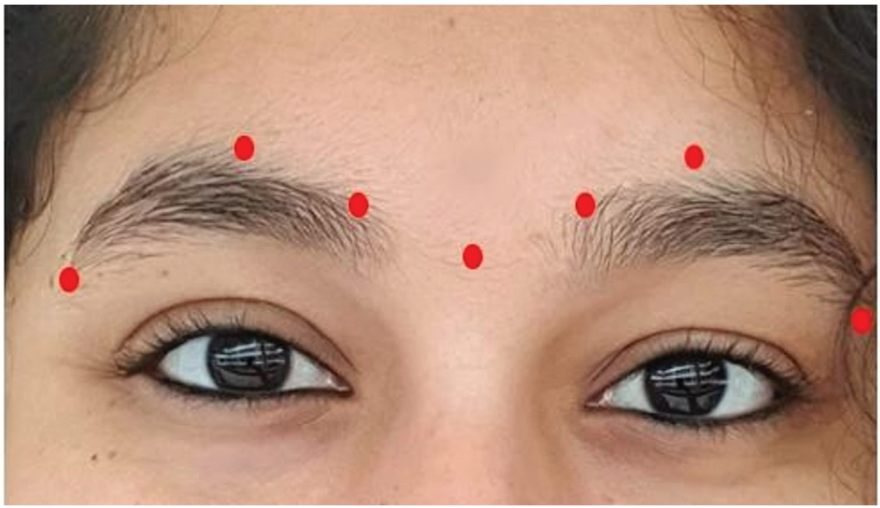

Figure 5.2D: Injection points for eyebrow lift

2. An initial dose of 20-30 IU in women and 40-60 IU in men is distributed among these injection sites.

3. The first injection is typically given in the belly of the procerus muscle (about 5-10 IU). This injection site can be marked as the center of the imaginary X that is drawn from the top of the medial eyebrow to the contralateral medial canthus of the eye.

4. The next injection sites are the belly of the corrugator supercilia, bilaterally, where about 7-10 IU in females and 15-20 IU in males is injected. The site for this injection is located directly above the medial canthus, just above the supraorbital ridge. The supratrochlear artery lies just medial to this injection site. Even though this landmark can be easily located above the medial eyebrow, the site should be chosen according to the bony and muscular landmarks regardless of the position of the eyebrow. To avoid excessive bruising, proper post-injection pressure should be applied.

5. The next injection site is located 1 cm above the supra-orbital ridge in the mid-pupillary line where about 4-5 IU of the toxin is used bilaterally. A common complication of injecting botulinum toxin at this site is ptosis of the upper eyelid. Hence, unlike other sites, firm massage post-injection should be avoided at this site, as it may cause diffusion of the botulinum toxin in the levator palpebral superioris muscle. The path of injection also plays an important role in avoiding this complication, and should be 1cm above the supraorbital ridge and should be injected in an upward direction intradermally.

6. For a more youthful appearance, lateral brow elevation is a common goal. To achieve this, some authors recommend an additional injection site to the standard pattern, at the lateral orbicularis oculi muscle. This is achieved by injecting around 7-10 IU of botulinum toxin intradermally just inferior to the lateral eyebrow. Care should be taken not to inject the lateral frontalis muscle as it is responsible for the elevation of the eyebrow. A record of the dose and site should be kept as individual responses to the treatment might vary. The result of botulinum toxin in brow lift is presented in Figure 5.2E.

Figure 5.2E: Showing Preoperative (a) and postoperative image (b) in patient treated with botulinum toxin.

Clinical tips

1. For patients with a long face, a more horizontal eyebrow is preferable. For this, a pronounced apex can be prevented with an injection at the mid pupillary line. In such cases, treatment of the lateral frontalis muscle can also be considered as it maintains the horizontal brow position, as an

increase in the resting tone of this muscle can cause eyebrow elevation. Contrary to this, for patients with a round face, a high arched eyebrow with lateral apex is preferred. For this, an additional injection to the standard injection pattern at the lateral eyebrow can help in the elevation. Consideration should also be given to the fact that while treating these patients for horizontal forehead lines, they will need the lateral frontalis to be left untreated so as to lift the eyebrow. For a diamond shaped face, a peaked eyebrow with more medial apex will make the face appear more oval. For this, it might be necessary to omit the injection that is given over the mid-pupillary line.

2. Lid ptosis: The risk of having lid ptosis is highest while treating at the mid pupillary line. Lateral brow injections can also lead to lid ptosis if the toxin diffuses into the levator palpebral superioris muscle.

Management of Eyebrow asymmetry

Eyebrow asymmetry can be commonly seen in the general population. Botulinum toxin proves an efficient non-surgical approach to correct these eyebrow asymmetries. The most basic approach is to raise the asymmetric eyebrow to match to the opposite side. Further adjustment of the dose and location can be done to achieve symmetry. However, it is difficult to find the right dosage to correct the asymmetry, hence, it has been suggested to start the treatment for asymmetrical eyebrows with the same botulinum toxin doses and then make adjustments at future visits accordingly.

Conclusion

Eyebrows play an important role in an individual's attractiveness, age and mood. Understanding the interplay of the muscles that affect the eyebrows can allow us to effectively alter and improve the position, height, and symmetry of the eyebrows with non-surgical methods, enhancing a person's appearance. Botulinum toxin is a simple, effective, and safe method to achieve this goal.

Learning points:
➢ Eyebrow shape and height plays an important role in attractiveness, emotional expressions and youthful appearance. An ideal eyebrow depends on various factors.
➢ The use of botulinum toxin in enhancement of brow height and contour has been well documented.
➢ Eyebrow asymmetry is a common problem and botulinum toxin treatment for the same is a simple, non-surgical method for correction.
➢ The standard injection pattern for the glabellar complex leads to inactivation of the eyebrow depressors and a portion of the lower frontalis, which causes compensatory increase in the resting tone of the frontalis muscle leading to brow elevation.
➢ The most common complication includes eyebrow ptosis and can be prevented by understanding the relevant anatomy.

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Chapter 5.3

Cosmetic Applications of Botulinum Toxin for the Management of Forehead Rhytids

Kumar Nilesh, Monica Patil, Aaditee Vande

Introduction

The horizontal lines on the forehead are caused by the contraction of the large forehead muscle (frontalis muscle). It is the major muscle that raises the eyebrow and the eyelids. Superiorly, the muscle is inserted in the galea of the scalp. The insertions of the muscle inferiorly include: the procerus, orbicularis oculi, corrugator supercilia, and the depressor supercilia. The detailed anatomy of the frontalis muscle is explained in Chapter 5.2. The action of the frontalis muscle results in contraction lines that are etched over time into the forehead. These forehead lines or forehead rhytids appear unaesthetic and are considered to be a sign of ageing. Over the past decade, the forehead has become a major target area for botulinum toxin injections in clinical cosmetology and dermatology. Botulinum toxin is injected into the frontalis muscle to reduce or eliminate rhytids.

Injection of botulinum toxin for management of forehead rhytids

Different injection points and dosages have been suggested in the literature for management of forehead rhytids with botulinum toxin. This can be explained due to individual differences in the frontalis muscle bulk and the forehead structure. Additionally, how the muscle is used functionally for facial expressions can be related to the difficulty associated with treating this region. In order to achieve effective results and to avoid complications, personalized injection techniques are required according to the type of forehead; either broad or narrow. For example, a broad forehead may require two or more horizontal lines of injections, while a narrow forehead may

require only one horizontal line of injections. In 2005, Ozsoy et al. reported a study on 990 patients with broad and narrow foreheads treated with botulinum toxin using different techniques.[1] In the study, tall/broad foreheads were classified as those whose greatest glabellar-frontal distance was more than 70 mm. Those less than 60 mm were classified as short/narrow foreheads. Three horizontal lines of injections were given for short foreheads, while three vertical lines of injections were given for tall foreheads. The author reported effective results in all patients without any complications.

In addition to the physical variabilities, there are also different types of botulinum toxin on the market made from different strains of bacteria, having different properties. The two most commonly used toxins available for cosmetic purposes are the onabotulinum toxin-A (Botox® cosmetic; allegran Inc., USA) and the abobotulinum toxin-A (Dysport®; Ispen Ltd, UK). Another report on a randomized, double blinded, split-face study of 24 patients was done to compare onabotulinum toxin-A and abobotulinum toxin-A for treatment of forehead rhytids and its effect on EMG (electromyographic) activity of the frontalis muscle.[2] After the injection, patients were observed for 20 weeks and longer-lasting effects were seen with abobotulinum toxin-A than that with onabotulinum toxin-A.

In 2004, Carruthers et al. published consensus recommendations for the use of botulinum toxin for the treatment of forehead rhytids.[3] Wide variations in the number of injection points (ranging from 2 to 12 sites) were suggested, with the majority agreeing on four and six injection sites. However, regardless of the number of injection sites, it is recommended that the injections should be given at least 1-2 cm above the supra-orbital rim to avoid the chances of brow ptosis (Figure 5.3A). It is also suggested to avoid the first horizontal rhytid above the eyebrow. The recommended dose ranges from 10-20 IU for women and 20-30 IU for men. It is important to clinically reassess the result two weeks following the injections to evaluate the eyebrow position and to determine the need for further treatment. However, in 2011, the consensus of Carruthers et al. was published that recommended almost half the earlier recommended dosage in the forehead, to gain a “natural relaxed look”.[4]

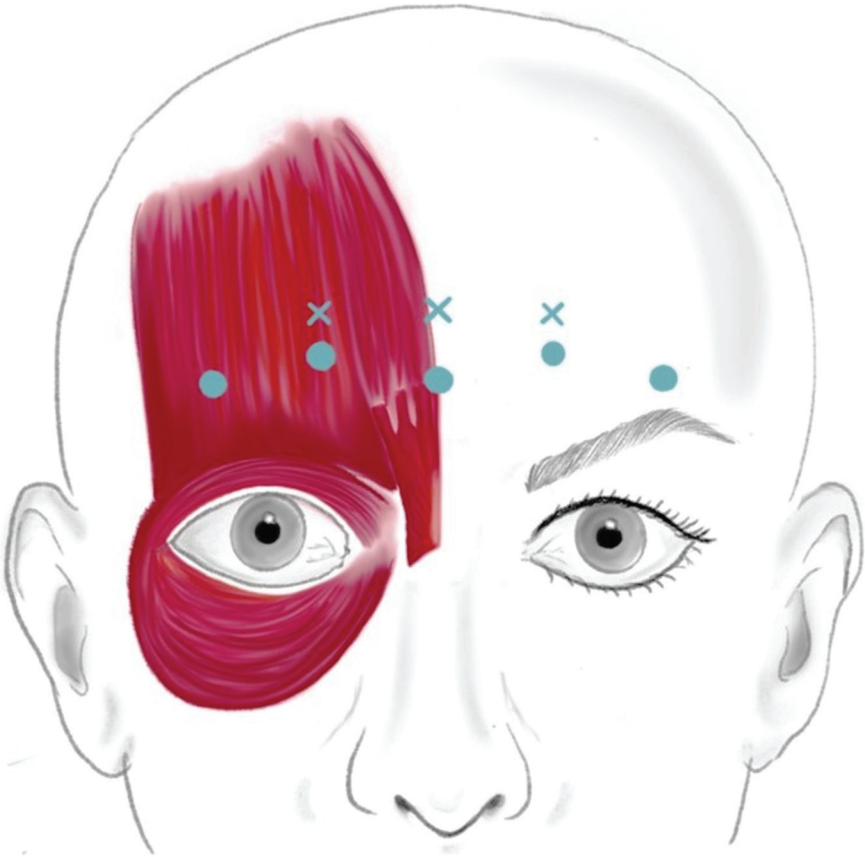

Figure 5.3A: Injection sites for forehead rhytids

According to consensus recommendations by Ascher et al., 2010:[5]

- It is recommended to use four to six injection points in a V-shaped pattern that should be slightly curved in women and straight in men. The lateral injection sites should be on the external orbital rim line.
- The injection should be given perpendicular and superficial into the frontalis muscle.

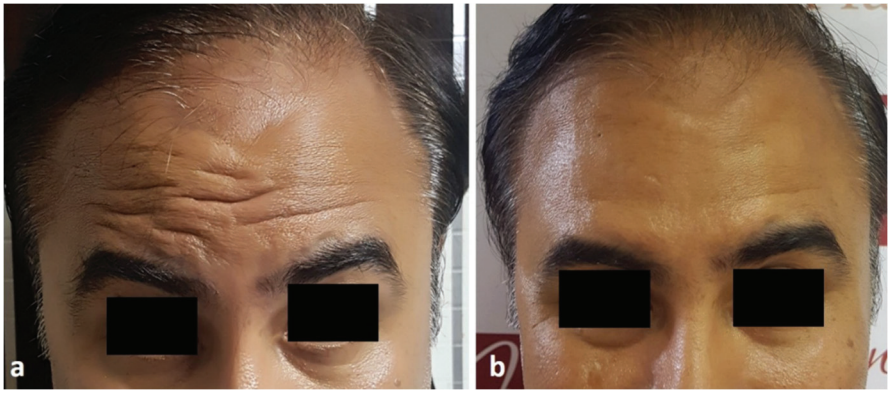

Figure 5.3B: Preoperative (a) and postoperative (b) images after treatment of forehead rhytids with botulinum toxin.

However, the V-shaped injection pattern can give an unnatural look and appear as the so called “mephisto look”. Therefore, depending on the frontalis prominence, positioning, and eyebrow shape, the injection pattern must be individualized. Figure 5.3B shows preoperative and postoperative photographs of a patient treated with botulinum toxin for management of frontal rhytids.

Complications

Potential side effects of the use of botulinum toxin for forehead rhytids include: pain at the site of injection, bruising, swelling, headache, eyebrow and eyelid ptosis, and diplopia. New rhytids may also appear as a side effect due to the overcompensation of the untreated adjacent muscles.

Conclusion

Botulinum toxin is an effective treatment option for treating forehead rhytids. However, to achieve the desired result with minimal complications, its use in this region requires careful individualized planning. Many techniques and guidelines have been published to improve the treatment approaches due to the significant variability of this region.

Learning points:
▪ Horizontal forehead lines can be safely treated using botulinum toxin.
▪ The frontalis muscle is responsive to treatment and, thus, low doses of toxin should be utilized initially.
▪ Injection techniques differ for individuals with tall (wide) and short (narrow) foreheads.
▪ New rhytids may appear as a side effect, due to the overcompensation of the untreated adjacent muscles, requiring retreatment.

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Chapter 5.4

Cosmetic Applications of Botulinum Toxin for the Treatment of Crow's Feet

Arun Kumar Panda, Monica Patil, Kumar Nilesh

Introduction

Patients frequently seek aesthetic rejuvenation for the periocular region. Age related changes of the facial skeleton and soft tissue, together with photo-damage of the periorbital skin can cause eyebrow ptosis, eyelid drooping, and lateral canthal rhytids (crow's feet), which results in the tired or sad appearance of a person. Crow's feet may start developing as early as the third decade of life and is a candid indicator of one's age (Figure 5.4A).

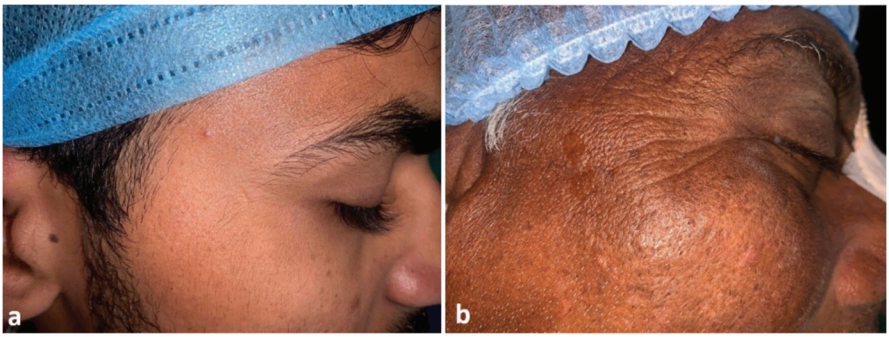

Figure 5.4A: Crow's feet in a young individual, which is barely noticeable (a), in contrast to an aged individual (b)

Eyes are considered to be an integral marker of physical attractiveness and beauty and an important component of facial recognition. A broad range of emotions can also be conveyed with subtle changes in the eyelid and eyebrow contour and position, even without any verbal communication. The clinician can achieve successful aesthetic facial rejuvenation by incorporating the

concepts of facial symmetry, sexual dimorphism, and aesthetic diversity, along with understanding the periocular anatomy and aesthetics.

Anatomy

The skin of the eyelid is one of the thinnest of the human body. It is elastic with no essential subcutaneous fat underlying it. Crow's feet are fine or coarse wrinkle lines that originate from the lateral ocular canthus and project outwards, in fan-like distribution. It can be appreciated most prominently during smiling or squinting. Factors that contribute to crow's feet may include smoking, lack of subcutaneous skin, redundant skin, and sun exposure. These rhytids can develop in the setting of the hyperkinetic muscle contractions of the orbicularis oculi that encircles the eye and functions in closing the eye. The orbicularis oculi muscle is aligned predominantly in vertical orientation at the lateral canthus of the eye, and is divided into three parts (Figure 5.4B).

1. **Lacrimal portion**: This portion of the muscle runs deep to the lacrimal sac and is inserted at the tarsal plates of the upper and lower eyelids. Contractions of this part of the muscle assist in tear flow by drawing the eyelids against the globe.

2. **Palpebral portion**: This is the innermost aspect of the muscle that passes superficial to the septum, extending from the bifurcation of the medial palpebral ligament to the lateral palpebral raphe. Contraction of this portion assists in the involuntary closure of the eyelid and blinking. The palpebral portion is divided into two components, the pre-septal and the pre-tarsal.

3. **Orbital portion**: It is the outermost portion of the muscle that overlies the bony orbit. It originates at the nasal process of the frontal bone, the medial palpebral ligament, and the frontal process of the maxilla. This muscle blends into the surrounding muscles; superiorly with the frontalis, the procerus, the corrugator supercilia, and the depressor supercilia. Inferiorly, it interdigitates with the Levator Labii Superioris, the Levator Labii Superioris Alaeque Nasi, and the zygomaticus major and minor muscles.

This muscle provides for forceful eye closure and depression of the eyebrow. It also contributes majorly to the formation of crow's feet. The zygomaticus major and minor muscles can be the contributing muscles to the inferior periorbital rhytids as contraction of these muscles superiorly elevate the skin in the periocular region.

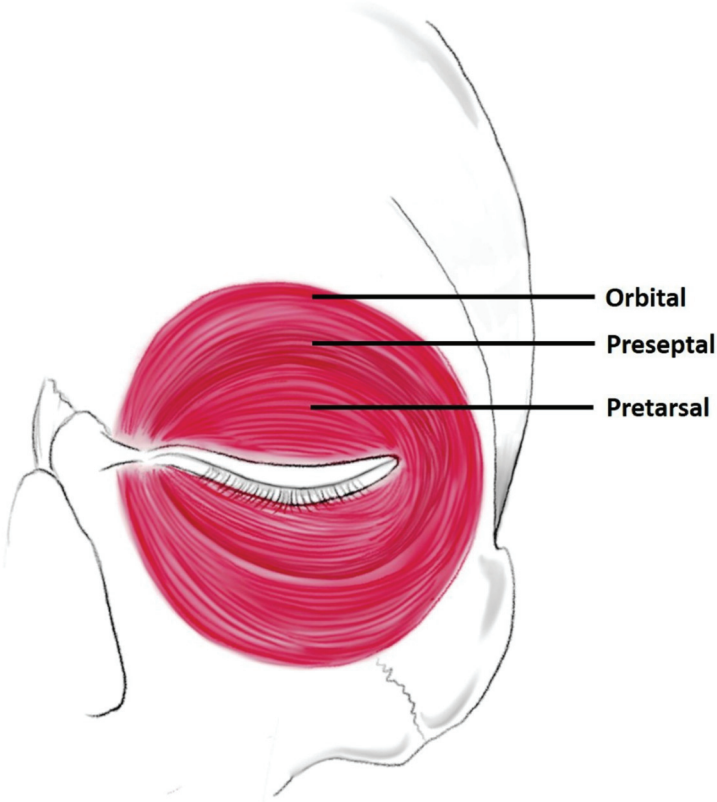

Figure 5.4B: Anatomy and parts of the orbicularis oculi muscle

Kane et al. identified four lateral canthal rhytid patterns that were formed due to the divergent muscle contraction patterns[1] (Figure 5.4C):

a. Fan shaped distribution of rhytids, extending from the upper eyelid to the upper cheek.
b. Rhytids of the lower lid or upper cheek.

c. Rhytids of the upper eyelid skin, extending down to the lateral canthus.
d. Central zone of rhytids confined to lateral canthus only.

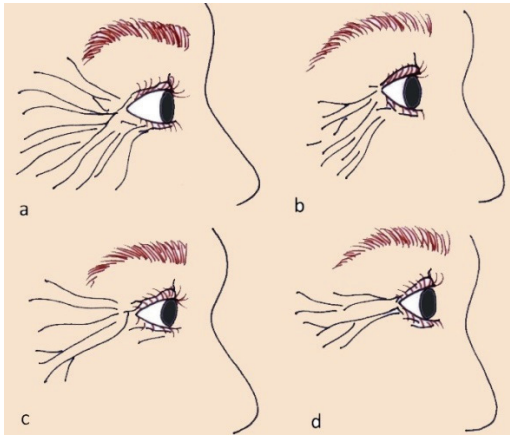

Figure 5.4C: Various typical crow's feet patterns

The youthful and the aging eye

Eyes are a very important part of non-verbal communication. Large and prominent eyes form the defining feature of facial recognition and beauty. Minor modifications of eye position and ocular muscle contractions can convey various emotions. Apart from the several factors that contribute to a youthful eye, maintenance of the volume of the area framing the eye is a central component. For this, the eyebrow should have enough volume and should be elevated and away from the orbital rim. The eye-eyelid complex should be outlined by a full and convex temple region laterally. The upper eyelid area below the eyebrow should not be deeply recessed, ideally showing only a few millimeters of upper eyelid. The eyelid crease over the upper lid-lash line should be prominent, and should run almost parallel to the lash line for an eye to look attractive. The lower eyelid should curve in a smooth convexity starting at the tarsal insertion. In a youthful face, there should be an absence of any kind of step-off or definite boundary between the cheek and the lower eyelid.

The aging process of the periocular region is characterized by a volume loss, a sunken or hollowed out appearance of the eye which

is surrounded by shadows and/or dark circles. Patient may have a tired, sad or malnourished appearance. Lateral brow ptosis can be seen due to the volume loss and skin laxity along with the weakening of the frontalis muscle, making the eyebrow sit flat against the orbital rim. Volume loss also causes drooping of the upper eyelid, inducing folds in the skin and shadows in the upper lid sulcus. In elderly patients, the visibility of the upper eyelid may be insignificant. As a part of the aging process, lateral canthal atrophy and associated lateral atrophy can also develop.

Pre-operative assessment

A detailed medical and surgical history should be obtained before botulinum toxin injection. It may help to plan any technique modification that may include prior facial surgery, including blepharoplasty, brow or face lift. Any previous injection of soft tissue fillers or botulinum toxin should be noted. At the first visit, a comprehensive evaluation of the periorbital complex should be undertaken that should include the eyebrows, eyelids, glabella, forehead, and lateral canthus. Any pre-existing asymmetries (brow ptosis, upper eyelid ptosis, globe prominence due to exophthalmos or orbital hypoplasia, variation of inter-canthal axis or tilt, lower eyelid position, scleral show, or differences in the malar prominence) should be pointed out to the patient and documented photographically prior to the treatment, in order to evaluate post-operative results objectively.

Along with that, any pre-existing ocular conditions such as persistent or intermittent tearing, dry eyes, or previous LASIK surgery may be associated with increased risk of dry eyes after botulinum toxin treatment. Any use of over-the-counter medications/eye drops for dry eyes should be noted. Any concern regarding decreased tear production that exists before the treatment can be resolved using Schirmer's test (*Figure 5.4D*). The tear production can be measured by placing a calibrated strip of filter paper within the lower eyelid. Another test to assess tear production is the rose Bengal test in which a dye is used to detect corneal scratches associated with dry eye.

Modifications may also be required in injection treatments around the eye in patients with systemic conditions with ocular manifestations including Grave's disease, Hashimoto's thyroiditis, and Sjögren's syndrome.

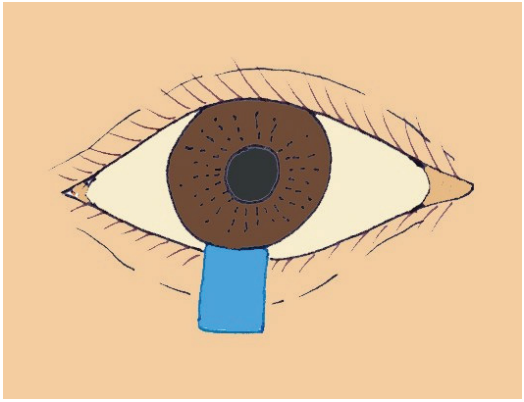

Figure 5.4D: Schirmer's test

The risk of development of ectropion or scleral show after infraorbital toxin injections can be estimated by the lower eyelid "snap-test" (*Figure 5.4E*). This is performed by gently pulling the lower eyelid downward and outward and then releasing quickly. A rapid return to the rest position without requiring an eyelid blink suggests a fully functional orbicularis muscle and a low risk of excessive eye rounding after botulinum toxin injections. A positive test shows a slow return to baseline, with the eyelid staying in a distracted position until the patient blinks, or until several seconds elapse and the lid very slowly resumes its normal apposition against the globe.

Figure 5.4E: Snap test to measure the lower lid laxity

An assessment of the lateral canthus rhytids is to be performed at rest, as well as when the patient is deliberately contracting the muscles. Both static and dynamic rhytids should be noted. Dynamic rhytids respond to a lesser extent to the treatment. A compensatory response to eyebrow ptosis may be seen due to horizontal forehead rhytids, due to the contraction of the frontalis muscle allowing eyebrow elevation.

All the findings should be carefully noted prior to the treatment, so that subsequent concerns are reduced and the toxin injections can be modified so that the baseline findings do not exacerbate.

Treatment:

1. While an injection in the periocular region is performed, the position of the patient should be upright or slightly reclined. The physician may stand on whichever side he or she feels comfortable. Some find standing on the same side as the

injection site more natural to work. However, others choose to stand on the opposite side so that the needle points away from the eye, while some prefer facing the patient from the front.

2. The injection site is prepared by cleaning with alcohol and the skin is slightly stretched to identify any superficial vessel along the area to be treated.

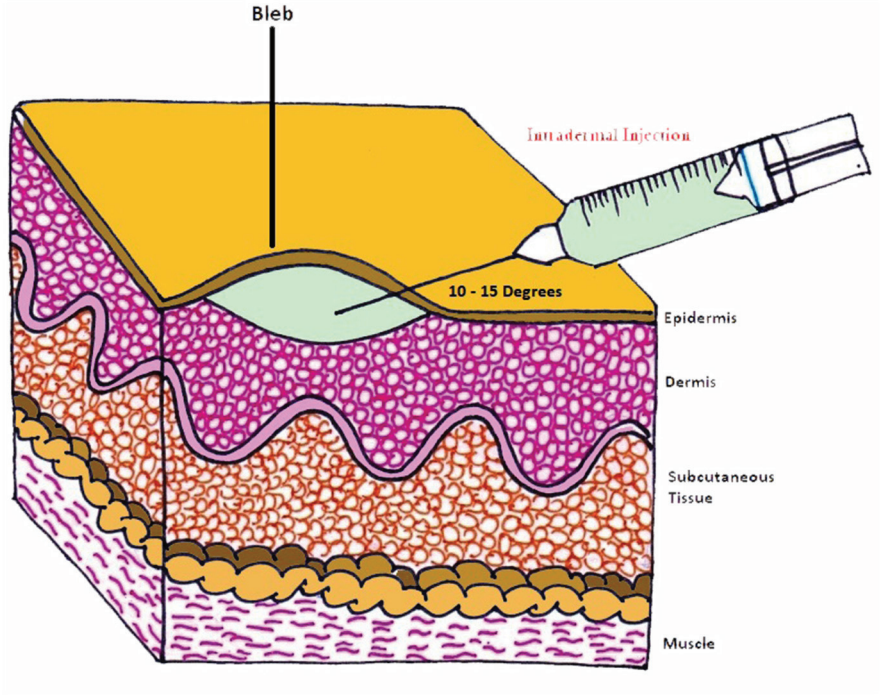

Figure 5.4F: Injection wheals illustrating the superficial placement of injection technique

3. Injections should be given slowly and meticulously and the needle should be changed frequently to prevent the needle from becoming blunt.

4. The injection is placed superficially into the dermis, to minimize the risk of ecchymosis (Figure 5.4F). The hand should be braced to avoid any unwanted sideways motion or

deep placement to avoid trauma and bruising.

5. The tip of the injection should be aimed to minimize the risk of spearing the globe. Some physicians prefer inserting the needle head-on vertically, while others prefer injecting tangentially to the skin, tenting the skin. Vertical injections are associated with a deeper placement than desired, while lateral injections are more confined to the dermis but have a risk of perforating small blood vessels.

6. A smaller volume has the advantage of precision with the prevention of migration. While more dilute solutions allow a wider range of action and reduce the number of injections required.

7. In standard crow's feet treatment, injection sites are commonly placed 1.5 cm away from the lateral canthus or 1 cm lateral from the orbital margin (Figure *5.4G*).

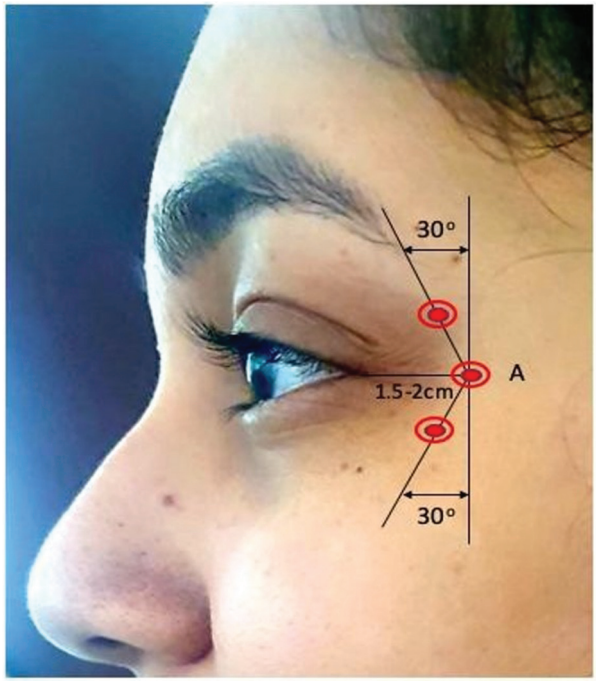

Figure 5.4G: botulinum toxin injection sites for crow's feet treatment

8. The injection pattern and dose is adjusted according to the patient's preference and according to the size and strength of the orbicularis oculi muscle.

9. A standard dose of around 6-18 IU of onabotulinum toxin-A is injected on each side at three to four injection sites along a 90-180 degree arc. As recommended in the studies by Matarasso and Lowe et al., each injection site is spaced at 1-1.5 cm distance.[2] Figure 5.4H shows the result of treatment using botulinum toxin.

In the trials by Lowe et al., the safety and efficacy of 6, 12, and 18 IU of onabotulinum toxin-A in treating crow's feet were studied and no statistically significant difference was noted in the efficacy or safety profile among the tested doses. In these trials, it was noted that four weeks post injection 95% of the patients in the 12 and 18 IU groups and 89% of patients in the 6 IU group showed improvement of around 1 point from the baseline on the facial wrinkle scale. It was also noted by these authors that a second injection of the same doses resulted in a longer duration of action.[3]

In a study, Ascher et al. evaluated the efficacy and safety of 15, 30, and 45 IU of abobotulinum toxin-A per side in the treatment of crow's feet. Four weeks after injection, the response rate at maximum smile was: 42% in the group injected with 15 IU, 60% in the group injected with 30 IU and 57% in the group injected with 45 IU of toxin, with an improvement in the severity of the rhytid with 1 grade from the baseline. This improvement was maintained for around eight weeks in the 15 IU group, and for around 12 weeks in the 30-45 IU group.[4]

In general, in women with minimal lateral canthal rhytids, a small dose of toxin is sufficient. However, certain men with a stronger muscle may need higher doses. In patients with protuberant globes, lower doses are preferred to avoid the risk of ectropion, or incomplete eye closure. Extreme caution should be taken when injecting in the lower malar crow's feet, especially in those blending with the diagonal rhytid of the mid- and lateral cheeks to avoid direct injection or spread of the toxin into the zygomaticus major and minor muscles, resulting in ipsilateral facial paralysis or lip ptosis. To prevent such complications, injection sites below the level of the superior zygomatic arch should be avoided.

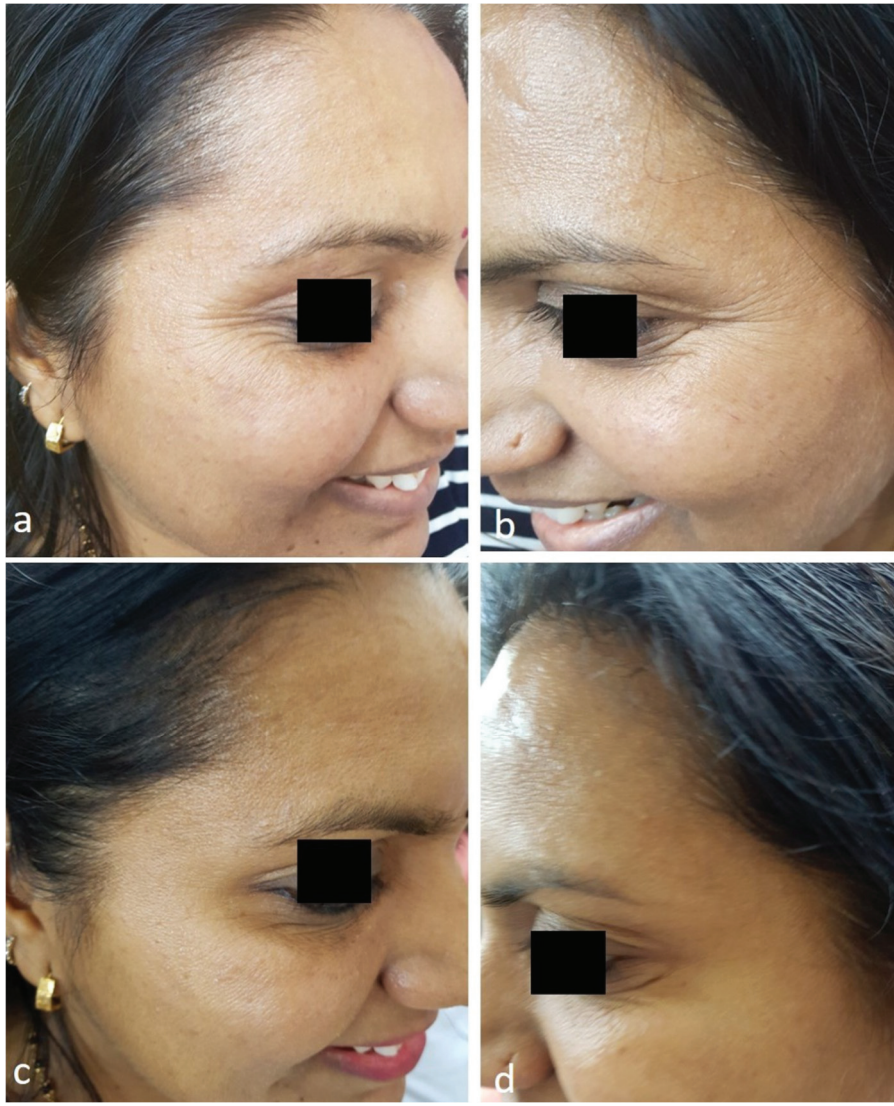

Figure 5.4H: Preoperative right (a) and left (b) and postoperative right (c) and left (d) images of treatment of crow's feet using botulinum toxin.

Complications:

- An immediate complication, as with all cutaneous injections, is pain. This can be reduced by using small needles, a slow rate of injection, gently rubbing or tickling the nearby skin, pre-treating with ice or topical anesthetic preparations, and reconstituting the toxin in preserved saline, rather than in unpreserved saline.

- The complications secondary to botulinum toxin injections in the periocular region are usually mild, self-limited, and quickly resolving. Complications such as eyebrow or eyelid ptosis are rare, and any temporary functional deficit tends to return to the baseline within weeks (long before the longevity of the toxins' period of action). Eyelid ptosis can be treated with alpha adrenergic drops. This stimulates the müller muscle which quickly contracts and raises the upper eyelid.

- Ecchymosis can be a complication occurring during, or after, injection. This is because of the thin periorbital skin. This can be prevented by using alcohol pads to help in identifying and avoiding vessels, or stretching the skin, superficial injections in the dermal planes and using a 31 or 32-gauge needle.

- Lip ptosis can also be seen, although rarely, as a complication of treating crow's feet. This can be a result of direct intramuscular injections or spread of the botulinum toxin in to the zygomaticus major and minor muscles, the Levator Labii Superioris or the Levator Labii Superioris Alaeque Nasi, as the fibers of all these muscles blend with the orbicularis oculi. There is no treatment for this complication. In 2002, Lowe et al. reported that muscles return to their normal function by six weeks post injection.[4]

Conclusion

Crow's feet can be safely and effectively treated with botulinum toxin. Optimal results can be achieved by appropriate patient selection and preoperative assessment. Injection techniques are standardized. However, it can be modified based on the patient's functional anatomy and the physician's preferences. Complications reported in this treatment are rare and, without exception, self-limiting and resolve spontaneously. Treatment of crow's feet with

botulinum toxin with adjunctive treatment modalities, such as laser resurfacing and hyaluronic acid fillers can give more comprehensive rejuvenation of the periocular space.

Learning points:
▪ Crow's feet can be safely and effectively treated using botulinum toxin.
▪ Preoperative assessment of the periocular region for analysis of dynamic and static rhytids, lower eyelid laxity, and upper eyelid ptosis, improves the precision and safety of the treatment.
▪ Schirmer's test can be used to assess the preoperative decreased tear production that existed before the treatment.
▪ A snap test can be useful for measuring the lower eyelid laxity.
▪ Injecting into the superficial vessels can be avoided by stretching the skin and side lighting.
▪ Injection discomfort, ecchymosis, and/or a spread into the nearby lip elevators can be avoided by superficial injection into the dermis.
▪ Complications secondary to botulinum toxin injections in the periocular region are usually mild, self-limited, and quickly resolving.

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Chapter 5.5

Botulinum Toxin in Periorbital Treatment

Kumar Nilesh, Monica Patil, Arun Kumar Panda

Introduction

Facial attractiveness is markedly defined by the periorbital region. Eyes are one of the most compelling features of the face, expressing a variety of emotions. The benefits of botulinum toxin were first noted in patients treated for strabismus and blepharospasms, and since then it has been used therapeutically in the treatment of cosmetic or functional improvement of the periorbital area. However, an in-depth understanding of the eyelid is very important for its treatment.

The key to a consistent and favorable outcome with botulinum toxin therapy is a proper understanding of the muscle anatomy as it relates to the volume and the three-dimensional nature of the face. The upper eyelid extends from the eyelid margin to the eyebrow superiorly. Approximately 8-11 mm superior to the eyelid margin, the superior palpebral sulcus is located extending between the medial canthus and the lateral orbital rim. The lower eyelid extends below the inferior orbital rim and joins the cheek. In a youthful face, the inferior palpebral sulcus is located 3-5mm from the lower lid margin (Figure 5.5A).

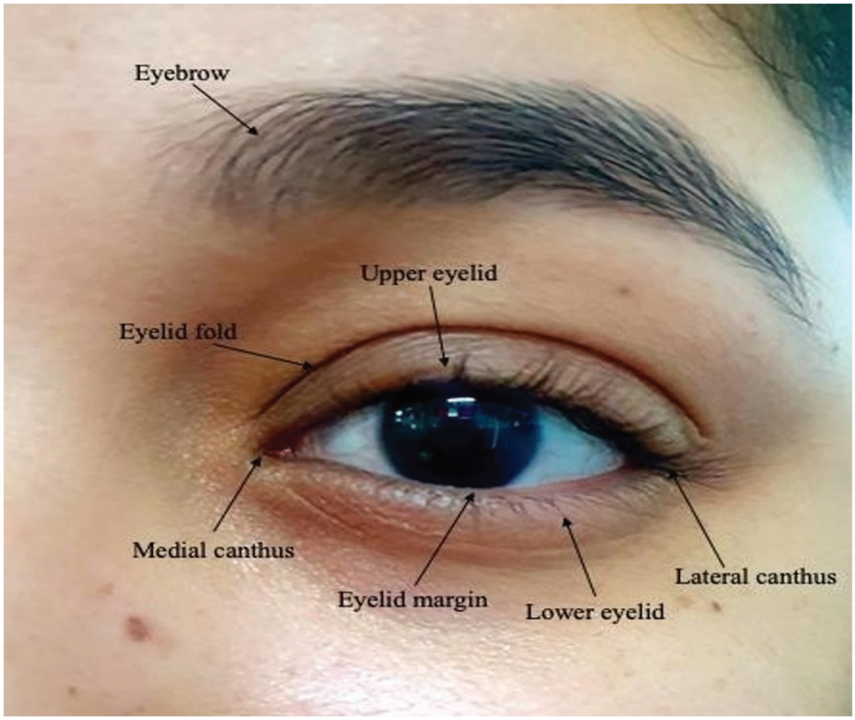

Figure 5.5A: Boundaries of the upper and lower eyelid

Aging of the periorbital region

The skin of the eyelid is the thinnest in the human body (<1mm) due to minimal subcutaneous fat. With aging, these delicate lids are prone to progressive stretching and thinning. The lower eyelid is usually subjected to fat redistribution, laxity, and weakening of the connective tissue. The smooth transition from the lower eyelid to the cheek becomes more prominent because of the puffiness, dark circles, or dermatochalasis under the eye. With aging, the orbital laxity, atrophy and pseudo-herniation give the eye a sunken appearance, while the radial wrinkles appear on the lateral aspect of the orbit.

Patient selection and assessment

Comprehensive assessment of the periorbital region of the patient along with patient education, counseling, medical and physical

examination should be done to avoid any post-injection complications. The treatment plan is determined based on the complete medical and ophthalmic history including previous history of any surgeries or rejuvenation procedures, and degree of rhytids and their potential response to the treatment. Besides this, the quality of the eye will also determine the treatment plan. Additional treatment may be required in patients with excessive skin above the eyes, prominent fat pads in the lower eyelids, and septal fat herniation. All findings should be noted and recorded in detail. The contraindications for treatment of patients with botulinum toxin should be ruled out (Table 5.5A).

Table 5.5A: Contraindications and precautions to periocular botulinum toxin treatment

Contraindication	Reason
Active infection or inflammatory skin condition at the site on injection	Severe elastosis (risk of scleral show)
History of neuromuscular disorders	Pre-existing conditions that may get worsened by the treatment
Use of aminoglycosides or other drugs that act at the neuromuscular junction	History of lower eyelid blepharoplasty stable or progressive muscular dystrophic conditions
Pregnant or lactating females	Body dysmorphic disorders and already-compromised function of orbicularis oculi.

Indications and techniques

Consensus recommendations have been developed for the dosing and techniques. However, treatment must be individualized according to the muscle treated and the desired outcome. Precise placement of the injections and conservative doses are important in the upper and lower eyelids to achieve beneficial results and avoid any adverse effects. An ultra-fine needle facilitates precise

periocular injections of botulinum toxin, with minimal pain.

Hypertrophic orbicularis oculi, infraorbital rhytids and widening of the eye

The concentric contractions of the orbicularis oculi muscle form the infraorbital rhytids that radiate below the eyes toward the cheeks. The lower eyelid bags form due to the hypertrophy of the pretarsal portion of the orbicularis oculi muscle. Conventionally, 2 IU of botulinum toxin is slowly injected sub-dermally in the lower eyelid. The injection is made 3 mm below the ciliary margin in the mid-pupillary line (Figure 5.5B). This relaxes and flattens the pretarsal orbicularis and improves the appearance of the lower eyelid.

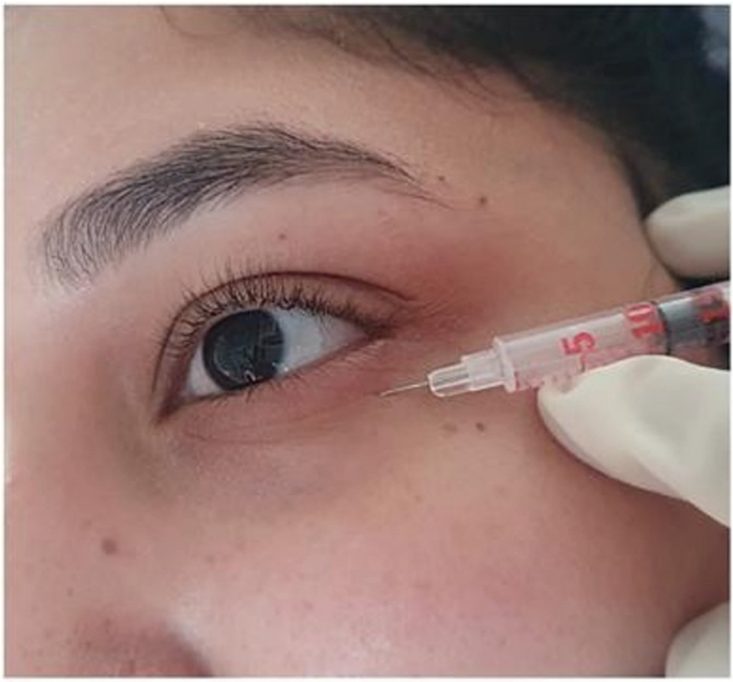

Figure 5.5B: Injection technique for lower eyelid treatment

Similar treatment in the lower eyelid, with concomitant treatment of the crow's feet can result in a more rounded appearance of the lower eyelid as it increases 2-3 mm of vertical palpebral aperture at rest and at full smile, respectively. Higher doses lead to an increase

in the side effects and do not lead to any further enhancement.[2] Therefore, a conservative approach with smaller doses is recommended for lower lid treatment, with retreatment after two to four weeks if required.

Eyelid ptosis, malposition, and asymmetry

Mild to moderate upper eyelid ptosis, malposition and eyelid-fissure asymmetry can be treated effectively with botulinum toxin. Correct placement, dosing, and careful patient selection can determine the predictability of the response. Low dose sub-dermal injection of botulinum toxin in the extreme medial and lateral aspects of the pretarsal region of the orbicularis oculi muscle just above the lash line allows an unopposed activity of the levator palpebrae and Müller's muscle, and its return to symmetry.

Similarly, lower eyelid symmetry and malposition (such as retraction, ectropion, and entropion) that have been previously managed with surgical intervention can be treated using botulinum toxin. This is done to tighten or shorten the horizontal length of the lower eyelid and symmetry with the contralateral side can be achieved. This malposition and symmetry can be restored by weakening the lower lid elevators on the side opposite to the lower lid retractions by two injections of botulinum toxin; one placed at the extreme lateral aspect of the lower eyelid and the second at the mid aspect of the lower eyelid pretarsal region, approximately in the mid pupil region that causes a similar retracted effect.

Doses in the upper and lower eyelids range from 0.5 to 1.5 IU per injection site. Higher doses are reserved for cases of lower eyelid hypertrophy and severe ptosis.

Conclusion

Rejuvenation of the periorbital region aims at targeting fine lines and wrinkles and at restoring the harmony and balance that is lost in the aging process. These goals can be achieved by botulinum toxin injections, alone or in combination with other cosmetic procedures around the eye. An in-depth awareness of the functional anatomy and interplay of the muscles of facial expressions, and careful screening of patients must be taken into consideration prior to the treatment by the injecting physicians to avoid adverse events due to misplaced injections, poor techniques, or inappropriate

patient selection.

Learning points:
▪ Successful periorbital rejuvenation requires careful patient selection, thorough exploration into the patient's desired outcomes and concerns, and a detailed medical and cosmetic history with comprehensive aesthetic assessment.
▪ For beneficial effects and avoidance of any adverse effects, precise placement of the injection and accurate dosing is important.
▪ Small doses in the lower eyelid can effectively minimize infraorbital rhytids.
▪ Eyelid ptosis and asymmetry can be corrected using botulinum toxin.

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Chapter 5.6

Applications of Botulinum Toxin for the Treatment of Perioral Lines

Monica Patil, Kumar Nilesh

Introduction

Rejuvenation of the perioral region can be very challenging. Treatment strategies in the lower face region are traditionally focused on volume restoration along with controlling the hypermobility of the muscles. For lower face rejuvenation, botulinum toxin is used as a monotherapy or as an adjunct to other procedures, such as dermal fillers, chemical peels, laser resurfacing, and face-lift procedures.

Anatomy

The lip unit/perioral region is one of the facial cosmetic units that extend from the base of the nose superiorly to the nasolabial folds laterally, and to the labio-mental crease inferiorly. The free edges of the vermillion borders sub-divide this region into the upper and lower lip and below the labio-mentalis crease there is another unit; that's the chin.[1] The upper lip is subdivided into the cutaneous upper lip, the vermillion upper lip, and the philtrum. The lower lip is subdivided into the cutaneous lower lip and the vermillion lower lip.

The perioral and the chin region are formed by a complex musculature. There are 12 facial muscles that affect the shape and function of the perioral area (Figure 5.6A). The perioral muscles can be classified according to their origins and insertions, as well as by their locations, with respect to the major structures.

Group 1: Muscles that insert into the modiolus:

The modiolus is located laterally and slightly superior to each angle of the mouth. It derives its motor nerve supply from the facial nerve

and its blood supply from the labial branches of the facial artery. The muscles under this group include: the orbicularis oris, the levator anguli oris, the zygomaticus major, the buccinator, the risorius, the depressor anguli oris, and the platysma.

Orbicularis oris: The orbicularis oris is a complex circular muscle which encircles the orifice of the mouth, forming the majority of the lips.

- *Origin:* From the deep surface of the perioral skin, the angle of the mouth, superiorly the median plane of the maxilla, and inferiorly the mandible.
- *Insertion:* Mucous membrane of the lips.
- Innervation: It is supplied by the buccal and mandibular branches of the facial nerve.
- *Actions:* The rima oris is closed by the tonus of this muscle. The lips are protruded by its phasic contractions and compressions. It also aids in mastication, expression, phonation, and the actions of whistling, sucking, and kissing. The orbicularis oris muscle is necessary for correct phonation, allowing for enunciation of the letters F, M, O, and P.

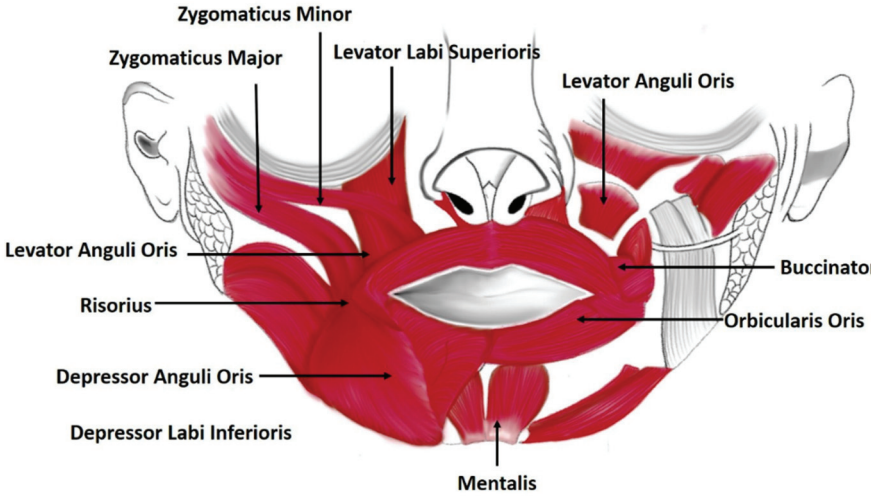

Figure 5.6A: Musculature of the lower face

Levator anguli oris: The levator anguli oris is a paired strap-like muscle of the face that is located above the angle of the lip.

- *Origin:* Arises from the canine fossa of the maxilla beneath the infraorbital foramen.
- *Insertion:* Modiolus
- *Innervation:* The buccal and zygomatic branches of the facial nerve.
- *Actions:* Elevates and medially moves the commissure of the mouth.

Zygomaticus major: Zygomaticus major is a thin paired facial muscle extending diagonally from the zygomatic bone to the angle of the mouth.

- *Innervation:* Innervated by the zygomatic and buccal branches of the facial nerve.
- *Action:* Upon contraction, this muscle elevates and laterally moves the commissure.

Buccinator: The buccinator is a thin quadrilateral facial muscle, and forms the main component of the cheek.

- *Origin:* The superior part arises from the outer surface of the alveolar process of the maxilla opposite to the third maxillary molar teeth. The inferior part arises from the buccinator ridge of the mandible, opposite to the three mandibular molar teeth. The posterior part arises from the anterior margin of the pterygomandibular raphe.
- *Insertion:* Modiolus, blends with the muscles of the upper lip.
- *Innervation:* Innervated by the buccal branch of the facial nerve.
- *Action:* Presses the lips and the cheeks to the teeth.

Risorius: The risorius arises from the parotid fascia and passes medially and anteriorly in a transverse plane to insert into the modiolus.

- *Innervation:* Buccal branch of the facial nerve.
- *Action:* Upon contraction, the risorius draws the commissure laterally and produces a sardonic smile.

Depressor anguli oris: The depressor anguli oris is a triangle shaped muscle with the vertex at the angle of the mouth.

- *Origin*: The fibers of this muscle originate from the oblique line of the mandible.
- *Insertion*: Its fibers blend with the orbicularis oris and insert into the corner of the mouth.
- Innervation: The marginal mandibular branch of the facial nerve.
- *Action:* This muscle depresses the angle of the mouth by pulling it laterally and inferiorly.

Platysma: Part of the platysma (Platysma pars modiolaris) that is posterolateral to the depressor anguli oris, deep to the risorius is included in this group. Along with the pars labialis, inserting into the muscles of the lateral lower lip, the platysma may be a significant depressor of the lower lip.

Group 2: Muscles that insert into the upper lip:

This group includes the muscles that originate from the maxilla below the infraorbital foramen and insert into the orbicularis muscle of the upper lip. The nerve supply is from the facial nerve, and these muscles act to elevate the upper lip. The muscles included in this group are: the levator labii superioris alaeque nasii, the levator labii superioris and the zygomaticus major.

Levator Labii Superioris Alaeque Nasi: The levator labii superioris alaeque nasi is a slender, strap-like muscle found on both sides of the nose.

- *Origin:* It arises from the inferior orbital rim on the maxilla, deep to the orbicularis oculi, and superior to the infraorbital foramen.
- *Insertion:* Fibers insert into the dermis of the upper lip and into the orbicularis oris.

- *Innervation:* It is innervated by the zygomatic and buccal branches of the facial nerve.
- *Action:* Upon contraction, the muscle elevates and everts the upper lip.

Zygomaticus minor:

- *Origin:* The muscle arises from the zygoma, deep to the orbicularis oculi and just lateral to the zygomaticomaxillary suture.
- *Insertion:* In the skin of the upper lip, medial to the zygomaticus major muscle.
- *Innervation*: It is innervated by the buccal branch of the facial nerve.
- *Action:* Upon contraction, the zygomaticus minor elevates and pulls the commissure laterally, which contributes to the nasolabial fold.

Group 3: Muscles that insert into the lower lip:

The muscles of this group originate from the lower border of the mandible and insert into the skin of the lower lip. The nerve supply is from the facial nerve, and they act to depress the lower lip. The muscles in this group include: the depressor labii inferioris, the mentalis, and the platysma.

Depressor labii inferioris: The depressor labii inferioris is a short quadrangular muscle found in the chin region.

- *Origin:* Originates from the anterolateral mandible and medial to the insertion of the depressor anguli oris.
- *Insertion:* It inserts into the skin and submucosa of the lower lip.
- *Innervation:* It is innervated by the mandibular branch of the facial nerve.
- *Action:* It acts by depressing the lower lip and also pulls it slightly lateral.

Mentalis: The mentalis muscle is a paired muscle, which acts as the primary muscle of the lower lip.

- *Origin*: The muscle originates from the body of the mandible.
- *Insertion*: It inserts into the orbicularis oris and the skin of the chin.
- *Innervation*: It is supplied by the mandibular branch of the facial nerve.
- *Action:* This muscle provides stability to the lower lip. Along with this, it helps in the elevation and protrusion of the lower lip (drinking), and the elevation of the skin of the chin (doubt).

Platysma: Part of the platysma (pars labialis) is included in this group. It is a paired sheet of muscle in the anterior neck region.

- *Origin:* From the fascia overlying the pectoralis major and deltoid muscles.
- *Insertion:* It inserts into the inferior border of the anterior mandible.
- *Innervation:* It is innervated by the cervical branch of the trigeminal nerve.
- *Action:* Its action is to depress the lip.

Perioral and chin aging

Radial perioral rhytids, a decrease in the vermillion fullness, inversion of the vermilion border, a downward turn of the oral commissures, a lengthened appearance of the cutaneous portion of the upper lip, chin dimpling, and a pre-jowl notch characterizes the aging of the perioral region.

The pathophysiology of the aging perioral and chin regions results in an aesthetically undesirable appearance and is multifactorial. Smoking and sun exposure are the potential extrinsic factors causing these changes. The facial ageing elements include decreased thickness and elasticity of the skin, decreased adherence between the skin and the subcutaneous tissue, sagging of the soft tissue, absorption of the fat, resorption of the skeletal element, and weakening of the muscles.

The first comprehensive study of facial aging elements was described in a paper published by Gonzalez-Uloa and Flores, in 1965.[2] The marionette lines are curvilinear wrinkles, extending down from the oral commissures to the jaw line. It may be a result of hyperactivity of the depressor anguli oris muscle, maxillary and mandibular resorption, and fat absorption. A prominent mentalis muscle can accentuate the horizontal labio-mental crease, accentuated with volume loss. It is produced by the depressor anguli oris and the mandibular ligament. The repetitive muscular actions of the orbicularis oris and volume loss contribute to the perioral rhytids. The perioral aging characteristics are enumerated in Table 5.6A.

Table 5.6A: Characteristics of perioral and chin areas
Prominence of nasolabial fold
Marionette lines
Radial perioral rhytids
Pre jowl sulcus
Vermillion atrophy
Prominence of labio-mental folds

Use of botulinum toxin for the upper and lower face

The goal for treatment of the lower face using botulinum toxin is to soften the wrinkles by muscular relaxation, rather than complete paralysis of the target muscle. The use of botulinum toxin in the orbicularis oris, the mentalis, and the depressor anguli oris muscles has gained popularity, as they directly affect the appearance of the perioral and chin regions with minimum complications. Treatment is contraindicated in patients who require precise enunciation and/or tight lips, for example in singers or public speakers. For the lower face, usually a combination of approaches is required and is seen to have better and long-lasting results.

Injection techniques:

Topical anesthesia should be applied over the target region before injecting. The target site is cleaned with alcohol pads and then the patient is asked to contract and relax the target muscle repeatedly. This helps to identify the target muscle.

Orbicularis oris:

Injection of botulinum toxin in these muscles helps in relaxing the muscles and thereby reducing the perioral rhytids and affords a slight increased eversion and exposure of the vermillion border. Injections in these muscles are placed superficially in the dermis, along or slightly above the vermillion border. Injecting close to the vermillion border reduces the diffusion of the toxin into the surrounding musculature, reducing the risk of complications. For the upper lip, it is suggested to start the treatment with 1-2 IU to up to 4 IU at four uniformly spaced sites. For the lower lip, it is advised to inject 1 IU to up to 2 IU, at two uniformly spaced sites (Figure 5.6B).

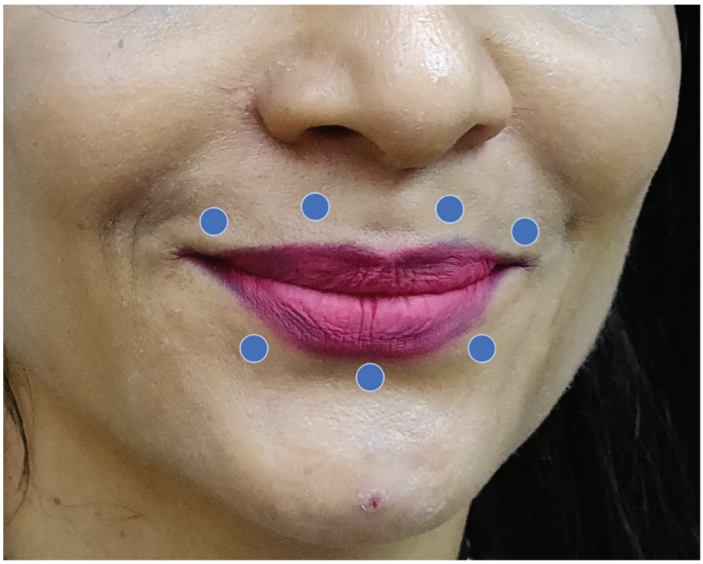

Figure 5.6B: Botulinum toxin injection points for the perioral region

Mentalis:

Chin dimpling and labio-mental crease prominence can be reduced by botulinum toxin injection in the mentalis muscle. Botulinum toxin injection is very effective in the treatment of chin dimpling in young patients. However, adjunctive filler treatment is necessary in patients with chin dimpling and a prominent labio-mental crease, as they are caused due to volume loss.

For injection into the mentalis muscle, 3-5 IU of botulinum toxin lateral to the midline at the chin's prominence is advised (Figure 5.6C).

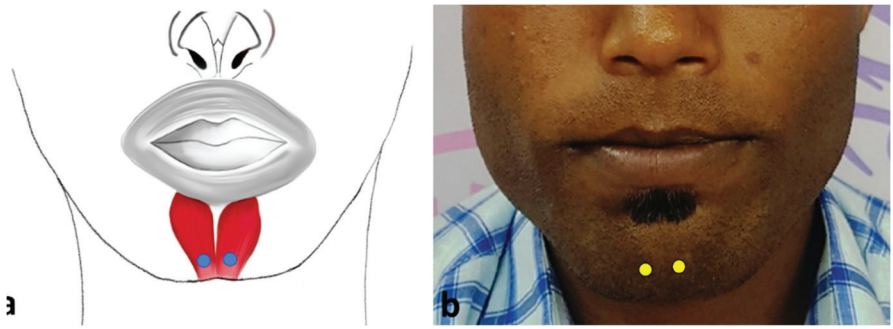

Figure 5.6C: Bilateral mentalis muscle with injection points for botulinum toxin.

Depressor anguli oris:

Botulinum toxin injections in the depressor anguli oris can reduce marionette lines, a downward turn of the oral commissures, and a long nasolabial fold. However, for better outcomes, fillers are generally required in treating these muscles.

Each muscle is treated with one injection into the middle third extending to the lower third of the muscle, where its fibers are numerous (Figure 5.6D). The injections should be given laterally to the oral commissures so as to avoid any effects on the buccinator muscle laterally. A 2 IU of the toxin should be injected at the inferior border of the mandible. It is advised to inject 4 IU on each side or 1-3 IU per side up to 7.5 IU per side.

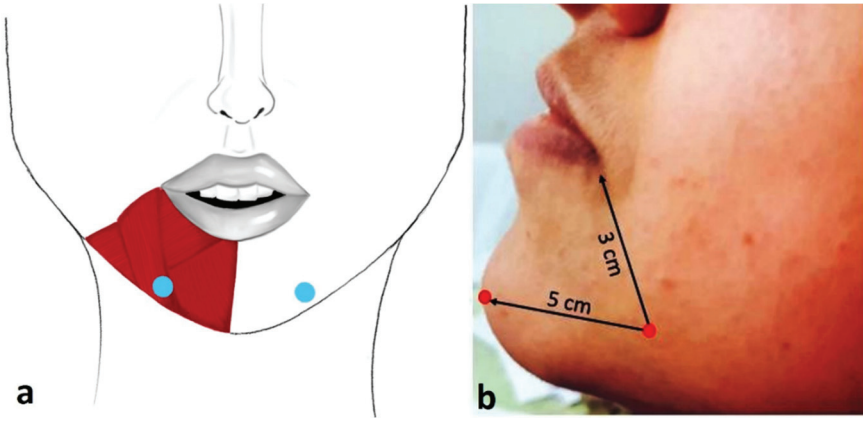

Figure 5.6D*: Points of botulinum toxin injection in the depressor anguli oris.*

Complications:

- *Orbicularis oculi:* Complications arising due to botulinum toxin injection in this muscle are lip asymmetry, difficulty with articulation or elocution, and inadvertent whistling. It may also result in difficulty in drinking and pursing lips or lengthening of the upper lip can be seen in some patients. These complications can be avoided by injecting just below the dermis so that the functions of the deeper muscle fibers remain unaffected.

- *Mentalis:* Paresthesia of the depressor labii inferioris may occur as a complication when the injection is placed too laterally, whereas paresis of the orbicularis oris results as a complication when the injection is placed too superiorly, affecting the speech or sphincteric functions.

- *Depressor anguli oris:* There may be a flattening of the contour of the lower lip as a complication when the injection is placed too medially, affecting the depressor labii inferioris. Injections that are placed too high can affect the orbicularis oris and cause problems with speech and suction, flaccid cheeks, an asymmetrical smile, and lower lip weakness.

Learning points:
▪ Radial perioral rhytids (smokers' lines or lipstick lines) characterize aging of the perioral and chin region.
▪ Age changes seen in the perioral region are: a decrease in the vermillion fullness, inversion of the vermillion, the lengthened appearance of the cutaneous portion of the upper lip, a downward turn of the oral commisures, a pre jowl notch or sulcus and chin dimpling, and marionette lines.
▪ Botulinum toxin softens the dynamic rhytids through muscular relaxation of the lower face instead of complete paralysis of the target muscles.
▪ Botulinum toxin in the lower face should be used with complete caution due to the complex muscular anatomy.
▪ Botulinum toxin can be used as a monotherapy in younger patients where the primary concern is fine, dynamic and/or static radial perioral rhytids due to muscular activity, and not volume loss.
▪ Complications can be avoided by injecting just below the dermis so that the function of the deeper muscle fibers remains unaffected.

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Chapter 6.1

Botulinum Toxin in the Management of Masseter and Temporalis Muscle Hypertrophy

Kumar Nilesh, Monica Patil, Eesha Pisal

Introduction

Masseter hypertrophy is a benign condition in which there is unilateral or bilateral enlargement of the masseter muscle.[1] The highest incidence for this condition is seen in the second and third decades of life, with no gender predilection.[2] The etiology of masseter muscle hypertrophy is unclear. However, most of the patients have an underlying clenching or grinding habit. Other conditions causing muscle hypertrophy are: temporomandibular joint disorders, bruxism, malocclusion, unilateral chewing because of loss of teeth or dental pain, and focal dystonia. The "work hypertrophy" theory of Gurney explains the asymmetric increase in the size of the muscles due to the patient's habitual unilateral over activity.[3]

Table 6.1A: Causes of masseter muscle hypertrophy
▪ Genetic factor
▪ Chewing habits (like chewing gum or dried food stuffs recurrently)
▪ Deleterious habits (like bruxism or clenching)

Clinical presentation

In masseter muscle hypertrophy, patients frequently complain of a dull aching pain deep within the masseter muscles. The pain can be

associated with temporomandibular joint dysfunction symptoms. Some patients may complain of lower face enlargement, with no history of facial pain. The enlargement can be unilateral or bilateral. Clinical examination reveals localized swelling over the ramus and angle of the mandible, unilaterally or bilaterally. The swelling when present unilaterally produces facial asymmetry. The swelling becomes more pronounced when the patient is asked to clench the teeth or chew (Figure 6.1A).

Differential diagnosis

Masseter muscle hypertrophy can be clinically misdiagnosed as: masseter space infection, soft-tissue tumor or an intra-bony pathology at the angle-ramus region of the mandible and parotid gland tumors. Whenever possible, a patient with suspected masseter hypertrophy must be subjected to an orthopantomogram to rule out any bony pathology. Ultrasonography can be useful in excluding soft tissue or salivary gland tumors.

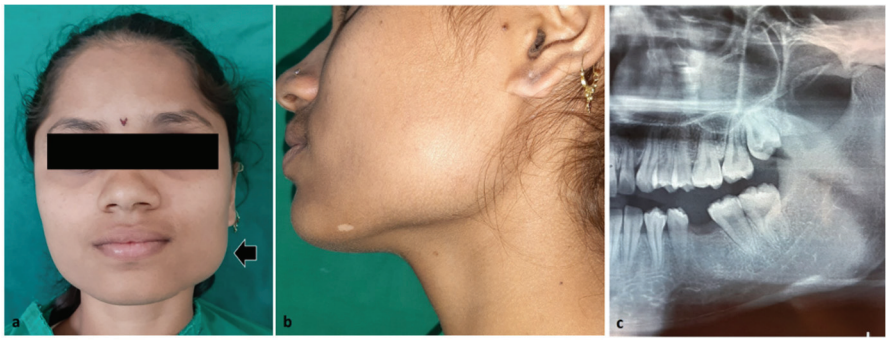

Figure 6.1A: *Photograph of unilateral* masseter hypertrophy involving *the left masseter muscle (arrow), resulting in facial asymmetry and presenting as a soft tissue bulge over the angle region of the mandible (b). The orthopantomogram of the mandible showed no intrabody finding, ruling out swelling due to underlying pathology (c).*

Management:

The traditional conservative, non-surgical methods of management of masseter muscle hypertrophy include: occlusal adjustment to correct dental imbalance, splint therapy, tranquilizers and habit

counselling. Surgical treatment for masseter muscle hypertrophy is masseter fiber resection and/or reduction of any bony hyperostosis in the angle-ramus region. Both procedures can be done through either an intra-oral approach or an extra-oral route. While the intraoral approach is aesthetically superior (with no scar over the skin), it provides compromised access to the masseter muscle and ramus of the mandible, requiring more sophisticated, contra-angled instruments and a bone cutting device such as a piezo-surgery unit. Extra-oral incision should be avoided, whenever possible, as it results in an incision scar over the face-neck region and is involved with risk of marginal mandibular nerve weakness. Medical and surgical management options in masseter hypertrophy are summarized in Table 6.1B.

Table 6.1B: Conventional treatment modalities of masseter hypertrophy

Medical	Surgical
▪ Counselling of patients with psychological disorders ▪ Mouth-guard in patients having habit of clenching or bruxism ▪ Anti-spasmodics and analgesics to relieve pain	▪ Masseter fiber resection ▪ Reduction of any bony hyperostosis in the angle-ramus region *Approach for surgery:* • Intraoral • Extraoral

Medical management may not be efficient in all the cases, especially those with severe muscle hypertrophy. Although successful, the conventional surgical treatment has limitations such as: risk of facial nerve injury, masseteric nerve damage, inferior alveolar nerve damage, or injury to the masseteric artery. Post-operative complications of surgery include: pain, swelling, trismus, hematoma, ecchymosis, and scar (with extraoral incision). If not executed with careful precision, asymmetric resection in cases of bilateral masseter hypertrophy can result in an unaesthetic appearance and patient dissatisfaction.

In 1994, Botulinum toxin type-A was first reported for the treatment of masseter muscle hypertrophy.[4] Local injections of small doses of the toxin in individual muscles can produce local paralysis. Selective weakening and atrophy of the muscle occurs as a result of this local paralysis, leading to reduction of the muscle bulk. Over recent years botulinum toxin has proven to be an effective alternative method to the conventional medical and surgical methods, with comparatively less or no unwanted effects on patients. However, a detailed knowledge of the anatomy of the muscle and associated structures is essential to minimize wrong injection sites and complications.

Anatomy

The temporomandibular joint complex is made up of bone, muscles and ligaments. The bony parts are comprised of the anterior part of the mandibular fossa of the temporal bone, the mandibular articular tubercle of the maxilla and the mandibular condyle. The ligaments include the articular capsule and disc, and a series of lateral ligaments. The four primary muscles of mastication associated with the joint are: the masseter, the temporalis, the lateral pterygoid, and the medial pterygoid.

Masseter muscle

The masseter muscle consists of three layers, all originating from the zygomatic arch and inserting into the ascending ramus of the mandible. This allows the function of the mandibular elevation to close the mouth.

The three layers of the masseter muscle include (Figure 6.1B):

1. *The Superficial part:* It arises from the zygomatic process of the maxilla and from the anterior two-thirds of the lower border of the zygomatic arch.

2. *The Middle part*: It originates from the deeper surface of the anterior two- thirds of the zygomatic arch and from one-third of the posterior arch.

3. *The Deep part:* It arises from the deeper surface of the zygomatic arch.

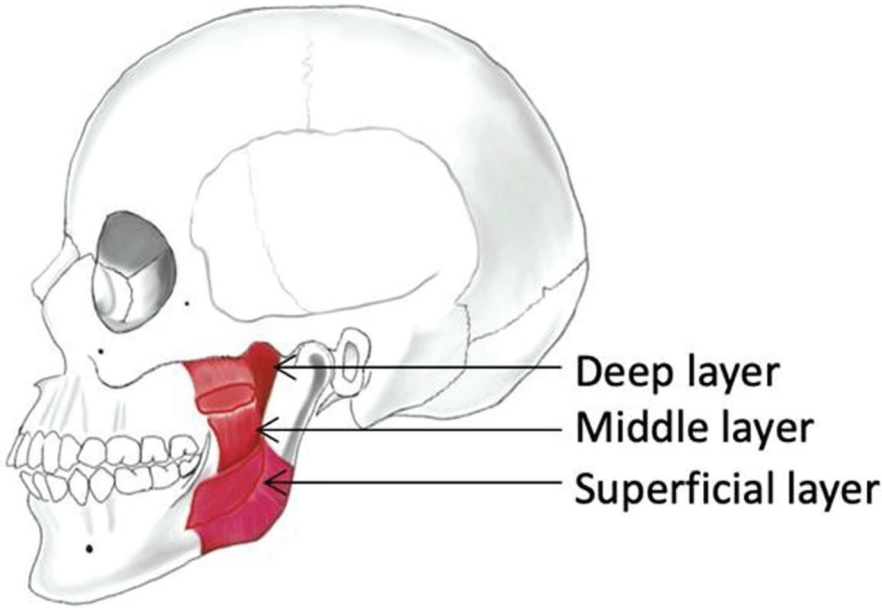

Figure 6.1B: Anatomy of masseter muscle

The fibers of all three layers merge as they pass downwards and backwards and insert into the lateral surface of the angle, the ramus and the coronoid process of the mandible. The region where all three layers overlap forms the thickest palpable region when the patient clenches their teeth. This maximum bulk is usually placed inferiorly near the jaw line.

Temporalis muscle

The temporalis muscle arises from the surface of the temporal fossa and the overlying temporal fascia. Its fibers converge down and insert at the apex, the anterior and the posterior borders, and the medial surface of the coronoid process (Figure6.1C). It functions to elevate the mandible. The posterior fibers of the temporalis retract the mandible.

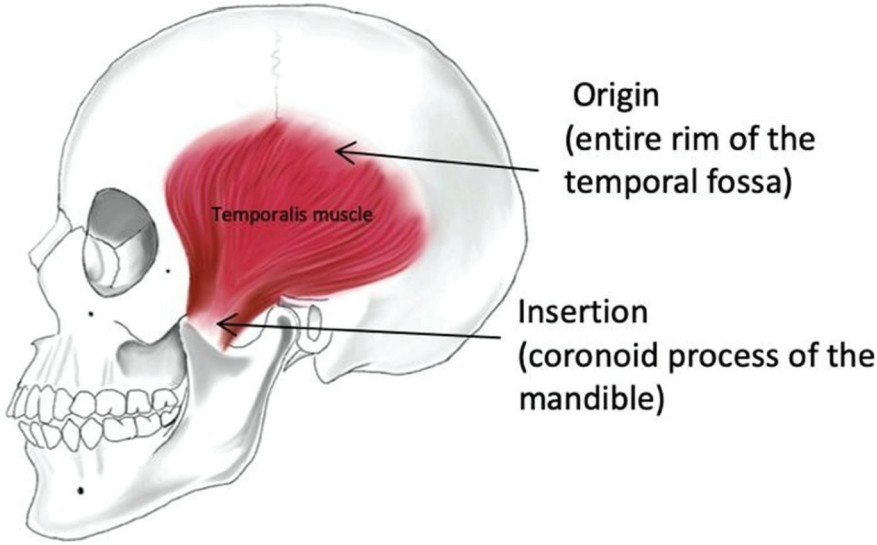

Figure 6.1C: Anatomy of temporalis muscle

Surface anatomy

The masseter muscle can be easily outlined at the superior border represented by the zygomatic arch, the inferior border represented by the inferior border of the mandible, and the posterior border by the posterior border of the ramus of the mandible. In patients with muscle hypertrophy, the anterior border is easily seen by asking the patient to clench their teeth. Anteriorly, the arterial pulsations are often palpated along the jaw line where the masseter muscle gives way to a gap. Superior to this, the hardness of the contracting masseter muscle may be differentiated from the softer connective tissue of the face anterior to the contracting muscle.

A knowledge of the surface anatomy and the trilaminar nature of the muscle is important for injecting into the masseter muscle. A bulky masseter muscle makes the face square-shaped and often becomes a negative influence in cases of female facial beauty. This is very common in East Asian patients, but may affect all patient groups. Aesthetic recontouring of the lower face initially developed as a concept with East Asian patients and has been recently applied in Western patients as well as all over the world. With this, there has been a gradual increase in botulinum toxin application in

treatment of muscle hypertrophy, promoting a better facial appearance.

Technique of masseter muscle injection:

The technique for injecting the masseter muscle is as follows:

- 100 IU of botulinum toxin is dissolved in 2 ml of normal saline. This yields a concentration of 5 IU per 0.1 ml of solution.
- The solution is drawn into a 1 ml syringe and is injected using a 32 mm long 30-gauge hypodermic needle.
- The masseter muscle is palpated by asking the patient to clench the teeth and the anterior and posterior borders of the muscle are palpated.

A line is drawn from the tragus to the angle of the mouth and at least 1 cm from the borders of the muscle. The injection sites are placed below this line to avoid injection in any other masticatory muscles, mostly super laterally and the salivary gland posteriorly and inferiorly (Figure 6.1D (a)).

- Depending on the muscle bulk, 3-5 injection points are selected at the site of the maximum bulge (Figure 6.1D (b)).

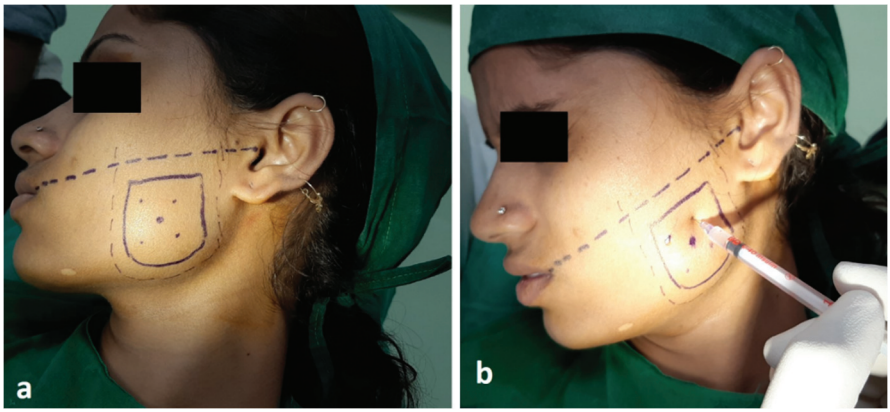

Figure 6.1D: Markings for the injection (a) and site of toxin deposition (b).

- The botulinum toxin is injected deep in the muscle to reach the deeper heads of the muscle. A superficial placement of the injection may result, when the patient is eating, in an appearance similar to a chipmunk chewing on nuts. This is due to the action of the functional deep head of the muscle pushing against a treated and flaccid superficial head.

Figure 6.1E: Pre and postoperative images in frontal (a, b) and profile views (c, d) showing the result of treatment of the left masseter muscle hypertrophy in a young female patient.

- The dose depends on the bulk of the muscle to be treated. However, 15-40 IU of botulinum toxin is usually required on each side.
- Injections should be repeated till the desired results are achieved at one to three month intervals and then reassessment should be done after three to four months.
- The results are promptly seen (Figure 6.1E) and the patients report readily with reduced clenching, morning headaches, sore teeth or other symptoms after the first session.
- Asymmetric masseter or unilateral masseter hypertrophy can be treated by altering the dosage. When hypertrophy is purely unilateral, it is suggested to inject some toxin on both sides, but more on the stronger, palpable and visibly bigger side.

Technique of the temporalis muscle:

Treatment of the temporalis muscle depends on various factors:

- If there are obvious signs of temporalis hypertrophy in the temporal fossa region while clenching or chewing.
- If the hypertrophy is not obvious at rest, injecting at the first session can be avoided. After the first injecting session, if it is similar to the masseter, the toxin should be injected, according to its bulk, in the areas of maximum projection.

Steps in technique for injecting into the temporalis muscle

- The temporalis muscle can be readily palpated superficially in the temporal area, as a fan-shaped muscle of variable size and depth, by asking the patient to clench (Figure 6.1F (a)).
- To adequately weaken this muscle, two types of injections are usually required (Figure 6.1E (b)).
- Superficial injection: Injection is given in the thinner upper regions of the fan shaped muscle. No special precautions are required in this area. However, advancing the needle too deeply may engage the bone and damage the needle.

- Deep injection: For the deep layer of the muscle, special anatomic consideration is required to note that the superficial temporalis fascia is approximately 1.5 cm superior to the zygomatic arch.

- Two penetrations are necessary in this area when using tactile sensation for penetration of the needle through the fascia as a guide for injection, as there are two superficial fascia layers with fat in between in this area, whereas the muscle is deeper. This injection is very useful because the muscle in this area is the thickest, before it inserts at the coronoid process of the mandible. Aspiration before injection is important as large vessels course through this field.

- **Dosage**: Dilution of 5 IU botulinum toxin per 0.1 ml normal saline is used. For treating the temporalis muscle, a recommended dose of 5-25 IU is divided into five injection sites.

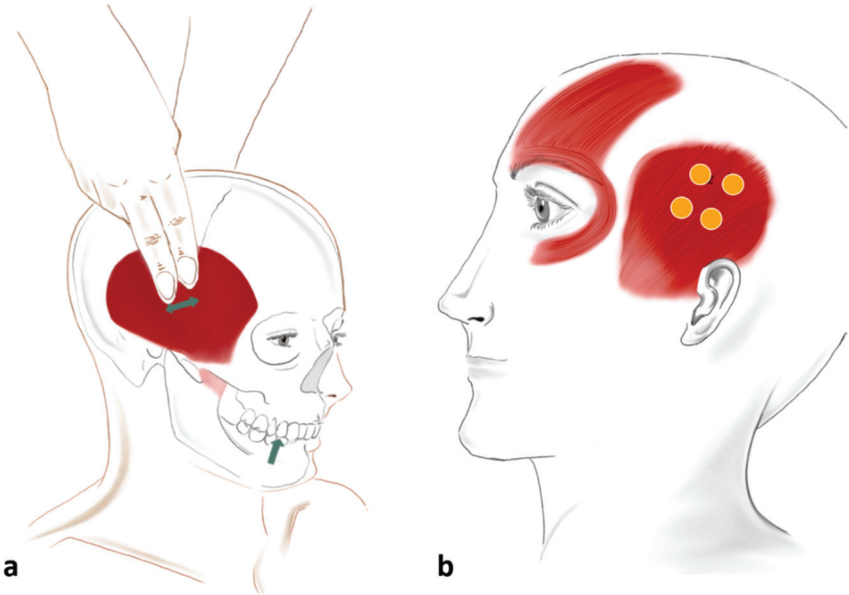

Figure 6.1F: Palpation of the right temporalis,as the patient clenches the teeth (a) and injection points for the temporalis muscle

Complications:

There are no permanent complications with the use of botulinum toxin in the management of masseter muscle hypertrophy. Some of the transient and minor complications include: altered smiling expression, sunken cheek, facial muscle weakness, pain at injection site and pain during mastication.

- Alteration in the facial smiling expression is as a result of injecting the toxin far too anteriorly, near the corner of mouth, into the zygomaticus major muscle (which is responsible for elevation of the corner of the mouth). Occasional drifting of the botulinum toxin in the anterior and superficial muscles, especially the risorius, can also limit the smile to some extent.
- A sunken cheek appearance may occur as a result of injecting the toxin very superiorly, below the zygomatic arch, leading to atrophy of the masseter muscle at its site of origin.
- In older patients, injecting in the large muscle bulk of the masseter can cause redundancy to develop anteriorly, resulting in jowling and sagging, because of the volume reduction of the skin that envelops the muscle.
- Over-hollowing of the infra-zygomatic and supra-zygomatic regions resulting in a haggard appearance.
- Rarely, intramuscular or subcutaneous hematoma and/or echymosis may be seen.
- Muscle bulging on mastication happens rarely and is easily avoided by deep injections.
- Pain, edema and itching at the site of injection can be seen in a few cases.
- Facial paralysis can be seen due to injection of the toxin into the substance of the parotid gland close to the branches of the facial nerve.
- Injection into the parotid gland may also result in reduced salivary flow.

The complications associated with masseter muscle injection are rare and recover with time once the effects of the toxin are reversed.

Conclusion

The masseter muscle is the seat of physical pain syndromes. Hypertrophy of this muscle can cause potential teeth damage. There are a set of medical conditions that may be treated using botulinum toxin. While treating the masseter muscle, it has been observed that there is a change in the facial shape, from square to triangular, which is more pleasing aesthetically. This has led to an important non-surgical alternative to reshape the lower face in a much similar way, providing one more indication of botulinum toxin in facial aesthetic management.

Learning points:

- Masseter hypertrophy is a benign condition in which there is a unilateral or bilateral enlargement of the masseter muscles.
- Even though the etiology of masseter hypertrophy is unclear, most of the patients have an underlying clenching or grinding habit.
- Other less common conditions causing muscle hypertrophy are: temporomandibular joint disorders, bruxism, malocclusion, unilateral chewing because of loss of teeth or dental pain, and focal dystonia.
- Local injection of botulinum toxin in the individual muscles can produce local paralysis and selective weakening, thereby leading to atrophy of the hyperplastic muscle fibers.
- Knowledge of the surface anatomy and the trilaminar nature of the muscle is important for injecting into the masseter muscle to reduce the risk of complications.

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Chapter 6.2

Application of Botulinum Toxin in Facial Palsy

Kumar Nilesh, Monica Patil

Facial palsy is a rare condition, which affects about 1 in 60 people during the course of their lifetime.[1] The clinical presentation of facial palsy includes: reduced wrinkles, less prominent nasolabial fold, drooping of the corner of the mouth, and drooping of the eyelid (Figure 6.2A). There will be inability to completely close the eye on the affected side leading to eye irritation and tearing. The imbalance of the facial muscle produces facial asymmetry and an unaesthetic appearance (Figure 6.2B). Lack of muscle balance between the two sides of the face also affects speech, swallowing and mastication. The clinical features of facial palsy are summarized in Table 6.2A.

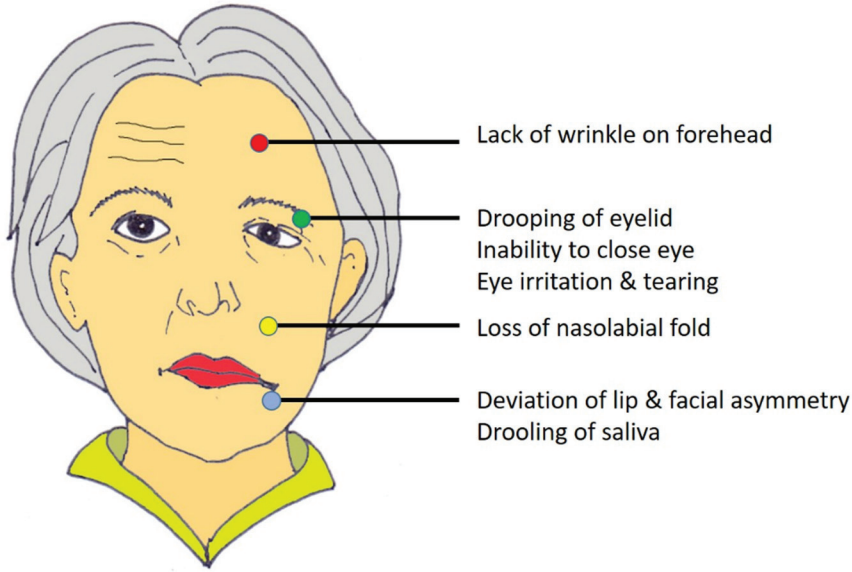

Figure 6.2A: Sketch highlighting the clinical features of facial palsy

Table 6.2A: Clinical features of facial palsy
▪ Loss of facial wrinkles, which is usually more evident on the ipsilateral forehead.
▪ Lack of prominent nasolabial fold
▪ Weakness (partial or total paralysis) of the facial muscles on the affected side
▪ Drooping of the eyelid on the affected side and inability to completely close the eye
▪ Dry eye (due to eye irritation from inability to completely close the eye)
▪ Epiphora (excessive tearing of the eye)
▪ Drooping of the corner of the mouth
▪ Difficulty in eating due to ipsilateral muscle weakness (food gets trapped on the affected side of the mouth)
▪ Drooling of saliva due to poor muscle control
▪ Impaired or loss of taste sensation on the affected side
▪ In case of involvement of the stapedius muscle there is increased sensitivity to sound (hyperacusis) on the affected side
▪ Altered sensation on the ipsilateral side of the face

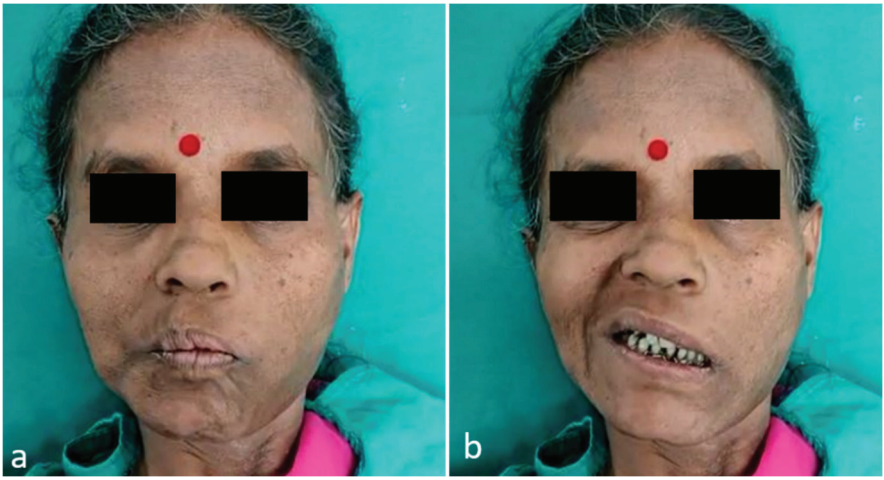

Figure 6.2B: Clinical features of facial paralysis; inability to puff cheek (a), drooping of corner of the mouth, facial asymmetry, and loss of nasolabial fold (b) on the affected side.

Almost half of the cases of facial paralysis are transient, and partial or complete recovery is seen within a few weeks. However, due to aberrant facial nerve regeneration many of these patients do not recover completely, and live with chronic sequelae which include: synkinesis, hyperkinesis, asymmetry and contracture.[1]

Synkinesis can occur in the due course of facial nerve regeneration on the affected side of the face. It is a neurological condition in which voluntary movement of a muscle causes involuntary contraction of other muscles. It involves muscles that typically contract together, for e.g., contraction of the orbicularis oculi (muscle around the eye) and the orbicularis oris (contraction of perioral-muscles) on smiling. Occasionally, an apparent muscle paralysis is caused by the contraction of the antagonist muscle at the same time (for e.g., paralysis of the zygomaticus major due to contraction of the depressor anguli oris or platysma muscle).

Hyperkinesis of the contralateral side muscles can be seen due to aberrant nerve activity or compensatory change on the unaffected side. Thus, the contralateral unaffected muscle responds with greater contraction, resulting in facial asymmetry. Initially the intensity of the contraction is low, but gradual worsening is seen

with time. In the early stages, hyperkinetic movement of the unaffected side of the face is seen during function, e.g., smiling or making other facial expressions. However, with time hyperkinetic movement occurs even during rest. This results in deviation of the face, including the lips, nose and eyes to the unaffected side. In advanced cases, and in patients with severe hyperkinetic action of the opposing muscles, facial rotation towards the hyperkinetic side is observed, along with a shortening of the soft tissue. These dysfunctions of the facial muscles result in considerable aesthetic and functional impairment and affect the overall quality of life of an individual.

Rehabilitation of facial paralysis aims to attain facial symmetry at both the static and dynamic stages. It should also achieve the desired control of the sphincters around the oral, nasal and ocular areas. The treatment should restore the facial aesthetics in rest and in function, as well as improve the functions of speech, swallowing and chewing. Conventionally, both medical and surgical methods of management are used. The medical management includes use of steroids, topical eye ointments and tear substitutes. The surgical modalities of management depend on the duration of facial paralysis i.e., acute (<3 weeks' duration), intermediate (3 weeks-2 years' duration) and chronic facial paralysis (>2 years' duration). Acute facial paralysis is mostly treated by the decompression of the facial nerve and facial nerve repair. Whereas, facial paralysis of intermediate duration requires nerve transfer procedures. Long standing or chronic facial paralysis typically requires local/regional or free muscle transfer. Hyperkinesis of the contralateral muscle(s) in facial palsy patients is treated by myotomy, myectomy and neurectomy.[1-3] Various static facial reanimation techniques are used for the correction of eyebrow ptosis, nasolabial fold modification, and external nasal valve repair. Use of implanted weights and suspensions are common for the correction of eye ptosis, for prevention of chronic eye exposure, and irritation. The conventionally used methods in the management of facial paralysis are listed in Table 6.2B.

Table 6.2B: Treatment modalities for management of facial palsy		
Medical management		
▪ Use of steroids ▪ Topical eye ointments and tear substitutes ▪ Antiviral drugs		
Surgical management		
Acute facial paralysis (<3 weeks duration)	Intermediate facial paralysis (3 weeks – 2 years duration)	Chronic facial paralysis (>2 years duration)
▪ Facial nerve decompression (transmastoid middle-fossa and translabyrinthine) ▪ Facial nerve repair (primary and cable graft)	▪ Cross face nerve grafting ▪ Nerve transfer (hypoglossal, masseteric spinal accessory)	▪ Regional muscle transfer (masseter, digastric, temporalis) ▪ Free muscle transfer (gracilis, serratus anterior, latissimus dorsi, pectoralis minor)

Use of botulinum toxin in treating facial paralysis

Botulinum toxin injection induced chemo-denervation causes temporary blockade of the acetylcholine release at the neuromuscular junction. This property of botulinum toxin can be used selectively for treating the hyperactive facial muscles. Synkinesis and hyperkinesis can be treated by targeting injections in the involved facial muscles. The muscles which most commonly need to be addressed include: the periocular, the perioral and the cervical muscles. The paralyzing effect on the injected muscle brings about the reduction of facial asymmetries caused as a result of facial palsy. It is used to address hyperkinesis and hypertony seen in patients both before and after the surgery. Injection of the toxin into the levator palpebrae muscle results in ptosis, which is utilized to protect the eye on the ipsilateral side from chronic

irritation. Besides its application to weaken the hyperkinetic side, it can also be used as a therapeutic test before neurectomies and myectomies.

Benefits & limitations

When compared with other methods, botulinum toxin presents a 100% rate of success in treatment of facial palsy. While various surgical modalities have been reported to provide about 90% success rate,[2] the use of botulinum therapy in the conservative management of facial palsy by controlling the action of the hyperkinetic and hypertonic muscle has potential to become the dominant therapy in the future. Although it is associated with minimal complications and a high success rate, certain limitations of the toxin therapy found for treatment with the different commercially available preparations of botulinum toxin should be considered. The limitations include: a short duration of effect, which usually last for three to four 4 months. This necessitates the use of multiple injections (two to three per year, depending on the severity of the condition and the dose administered), which further increases the cost of the therapy. The possibility of primary or secondary immunological resistance and specific side effects, depending on the injection site, should also be kept in mind. The advantages and limitations of botulinum therapy in the management of facial palsy are summarized in Table 6.2C.

Table 6.2C: Advantages and limitations of botulinum therapy in the management of facial palsy

Advantages	Limitations
▪ High success rate	▪ Temporary effect
▪ Less invasive, compared to surgery	▪ Need for repeated injections
▪ Tailored to patient's need (dose and no. of injections) based on the degree of involvement	▪ Allergic response, injection site irritation, hematoma, reaction.
▪ Residual defect can be corrected by reinjection	▪ Cost of therapy

Technique of use of botulinum toxin:

The muscles to be injected by botulinum toxin depend on the extent of the facial palsy. Often the muscles which need treatment include: the zygomaticus major, the zygomaticus minor, the levator labi superioris, the levator labi superioris aleque nasi, the depressor anguli oris, and the depressor labii inferioris (Figure 6.2C). Knowledge of the anatomy, attachment and insertion of the muscles is essential for injecting into the respective muscles. For confirmation of the anatomical landmarks, the patient is asked to contract and relax the involved muscle by making a particular facial expression. The muscle bulk should be palpated before injecting the toxin.

The dose/volume of botulinum toxin used varies depending on the degree of hyperkinesis or hypertony of the involved muscle, and the severity of the facial asymmetry. However, the guideline for the estimated dose of injection into the respective muscle is summarized in Table 6-2D.

Table 6.2D: Management of facial palsy using botulinum toxin

	Muscle treated	Landmark	Dose
1	Zygomaticus major	at their points of origin	4 IU
2	Zygomaticus minor	at their points of origin	2 IU
3	Levator labii superioris	at the orbital margin	2 IU
4	Levator labii superioris alaeque nasi	at the level of the nasal arch	2 IU
5	Modiolus area	0.5 cm from corner of the mouth	4 IU
6	Risorius	2 cm from corner of the mouth	6 IU
7	Depressor anguli oris	5 cm from corner of the mouth	6 IU
8	Depressor labii inferioris	1 cm from the mucosa transition	4 IU

Results of the treatment start to appear by the second to third day after injection. However, it is only by the 15th day that the correction of the facial asymmetry reaches its peak.

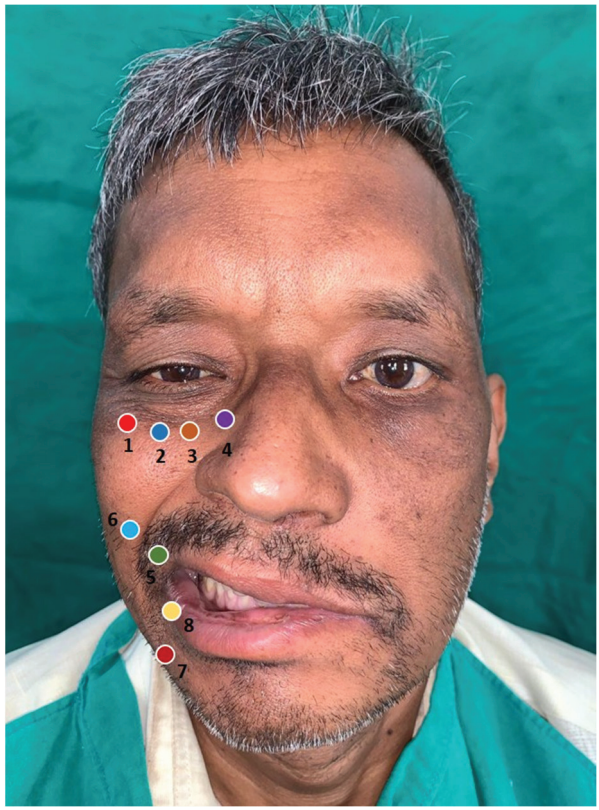

Figure 6.2B: Injection for botulinum toxin in management of facial palsy

Conclusion

Botulinum toxin injection is a minimally invasive technique that is useful in restoring the facial symmetry at rest and during movement in chronic as well as acute facial palsy. Although the result is temporary, requiring repeated injections, it avoids the invasive surgical procedure conventionally used in its management.

Learning points:
➢ Botulinum toxin can be used to reduce asymmetries and control the hyperkinesis and hypertony in patients with facial palsy, both before and after surgery, as well as an independent treatment modality in selected cases.
➢ The dose of botulinum toxin is determined by the severity of the facial palsy and the extent of involvement of the muscles.
➢ When compared with other methods, botulinum toxin shows a 100% success rate, with much fewer adverse events.
➢ The effect of therapy usually starts by the 2-3rd day and attains maximum effect by the 15th day. The correction lasts for about 4-6 months, requiring reinjection. (2/3 per year)

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Chapter 6.3

Role of Botulinum Toxin in Pain Control in Trigeminal Neuralgia

Monica Patil, Kumar Nilesh

Introduction

The International Association for the Study of Pain defines trigeminal neuralgia as "sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial (trigeminal) nerve."[1] The episodes of pain in trigeminal neuralgia significantly reduce the quality of life for patients. The pain is typically localized over the region of distribution of one or more divisions of the trigeminal nerve, with the mandibular branch being the most commonly involved. The pain is precipitated on minor touch or movement of the region supplied by the nerve or its branch. These areas are known as *trigger zones*.

The initial treatment of trigeminal neuralgia is pharmacologically with long-term anticonvulsant therapy. Oral carbamazepine is the first line of therapy in the management of this condition. However, in due course it can be ineffective, or can lose its potency over the period of therapy. About 20-50% of cases become resistant to medicinal therapy. Surgical management of trigeminal neuralgia is necessitated in case of refractory disease. The surgical management includes various peripheral and central procedures, and vary from central trigeminal root decompression to peripheral neurectomy of the involved branch or branches. Although more invasive, surgical management remains the only option for management of the severe and often debilitating pain in trigeminal neuralgia refractory to the medicinal therapy.

Along with the use of botulinum toxin in cosmetology, it has also been ound to be effective in pain management in cases of painful dystonia and cervical torticollis.[2] In 2002, Micheli et al. first reported

significant improvement in trigeminal neuralgia, while treating a case of hemifacial spasm combined with trigeminal neuralgia, using botulinum toxin.[3] Subsequently, multiple reports and clinical studies have been published on the use of botulinum toxin in management of the pain in trigeminal neuralgia.[4,5] Although there is a gradual decline in the effectiveness of pain control due to the short-term effect of the toxin, subsequently requiring revision injections, botulinum toxin can play an important role in treating trigeminal neuralgia in the future.

Mechanism of action

The mechanism of botulinum toxin for pain control in the treatment of trigeminal neuralgia is not fully understood, and is an area of further research. Various studies have been conducted to understand the analgesic potential of botulinum toxin, for its possible application in trigeminal neuralgia.[7-8]

Once the toxin is deposited into the subcutaneous or submucosal tissue, the peripheral terminals of the nerve fibers (type C) pick it up by endocytosis. The toxin molecule is then transported in a retrograde fashion, to the trigeminal ganglion and centrally to the spinal trigeminal nucleus. It is believed that the pain-relieving action of botulinum toxin is brought about by its ability to block the transport of nociceptive input at the nociception modulating centers. It blocks the release of nociceptive neurotransmitters at the preganglionic and postganglionic synaptic terminations, blocking the release of norepinephrine and adenosine triphosphate, bringing about pain relief. Association of botulinum toxin has also been seen with the inhibition of formalin-induced release of glutamate from primary afferent terminals.[7, 8] It is also hypothesized that the sensitization of the peripheral nociceptive nerve is prevented by pre-treatment using botulinum toxin, thus controlling the neuralgic pain.

Literature review

The first case of successful management of trigeminal neuralgia was reported by Micheli et al., in 2002. Since then, about ten well designed clinical studies have been published in the PubMed English literature over the past decade.[4, 9-17] With promising success rates, varying from 70 -100%, use of botulinum toxin is only expected to become more popular in the future. The review of the

literature is summarized in Table 6.3A.

Site of Injection

Most of the authors advise injections of the toxin in the area of pain, as localized by the patient (in the area of distribution of the involved branch of the trigeminal nerve). The injections are made in the subcutaneous plane (depth of injection 1-3 mm) and are spaced at a distance of 10-15 mm. When pain is present at the intraoral site, submucosal injections are advised, using the same protocol as for subcutaneous injection. Injection at trigger zones, either independently or along with injections in areas of pain localization, have been advocated by multiple authors.[4, 13, 15, 16] Batifol et al. compared the results of botulinum toxin injections made in areas of pain versus those made in the trigger zones. Injections made in the areas of pain showed a success rate of 100%, as compared to 83% in the trigger zone group.[16] The dose of botulinum toxin required in the trigger zone group was comparatively low. However, the statistical comparison between the two areas treated did not show any significant difference. Zúñiga et al. advised additional injections in the masseter muscle when the mandibular division was involved. Recently, injections into the main nerve trunks of the mandibular and maxillary divisions of the trigeminal nerve have been reported with a higher success rate of about 89%.[17]

Dose of botulinum toxin

The dose of botulinum toxin used in the management of trigeminal neuralgia ranges from 20 to 100 IU. Zhang et al. reported a reduction in the pain score by 70.4% with a dose of 25 IU as compared to 86.2% when 75 IU of botulinum was injected. Turk et al. injected a higher dose of 50 IU of botulinum toxin in each nerve truck of the maxillary and mandibular divisions of the trigeminal nerve, and reported better pain control, with a success rate of 89%.[17]

Table 6.3A: Review of published studies in literature				
Author & year	**Patient no. & Dose**	**Method**	**Result**	**Side effects**
Borodic et al. 2002[9]	11 25-75 IU	Subcutaneous injection in the area of pain as localized by the patient (spaced at a distance of 10 mm and depth of injection 1-3 mm)	73% (for period of 2-4 months)	Transient facial asymmetry, erythema, edema at the injection site
Turk et al. 2005[10]	8 100 IU	Subcutaneous injection in the area of the zygomatic arch	100%	Mild transient facial asymmetry.
Piovesan et al. 2005[11]	13 25-75 IU	Subcutaneous injection among the trigeminal nerve branches	31% were pain free & 69% had > 50% reduction in the medication dose	Transient facial asymmetry
Z ú˜niga et al 2008[4]	12 20-50 IU	Subcutaneous injection in the trigger zone area, For mandibular involvement, additional injections in the masseter muscle	83% showed reduction in pain.	Transient facial asymmetry.
Wu et al. 2012[12]	42 75 IU	Intradermal or submucosal injection in the area of pain distribution.	68.18% patients (at 8 weeks)	Transient treatment related adverse effects.

Shehata et al. 2013[13]	20 40-60 IU (5 units at each trigger zone)	Subcutaneous injections at the trigger zones.	Significant pain reduction (at 12 weeks)	Transitory and minor facial asymmetry, hematoma, itching and pain at the site of injection
Zhang et al 2014[14]	4 25 IU to and 75 IU (in 2 groups)	Subcutaneous or submucosal injections in the areas of pain. Injections at 20 points, (0.05 ml per point)	Reduction in the pain scores; 25 IU group (70.4%) and 75 IU group (86.2%)	Mild transient facial asymmetry, edema at the injection site
Xia et al. 2016[15]	87 -	Subcutaneous injection at the sites of pain and trigger zones (15-20 injection sites, separated by15 mm, depth of injection 0.1 cm)	80.46% (at 8 weeks)	Transient local swelling, muscle relaxation at the injection sites
Batifol et al. 2016[16]	28 15-50 IU	Injection into the areas of pain (versus) injection in the trigger zones	100% (pain area group), 83% (trigger zones group)	NA
T¨urk et al. 2017[17]	27 100 IU	Injection into the main nerve trunks of the mandibular and maxillary divisions of the trigeminal nerve	88.9% success rate (at 8 weeks)	Transient facial weakness, masseter weakness

Side effects and limitations

Most of the side effects of botulinum toxin therapy are mild to moderate in severity and transient in nature. The most common side effect seen in reported studies include reversible mild facial asymmetry, evident on function. Static facial weakness may also be present and is usually due to diffusion of the injected dose of botulinum toxin into the adjacent facial muscle(s). To avoid the facial muscle, the injection should be made in the subcutaneous and submucosal plane, with the depth of insertion not exceeding more than 0.1 cm.[15] Other minor side effects of the therapy include: local swelling, edema, itchiness, redness, haematoma and pain at the site of injection. These complications are mild to moderate and self-limiting, with resolution seen within a few days or weeks.

An important limiting factor of botulinum toxin therapy in managing the pain of trigeminal neuralgia is its temporary effect, which lasts for about 60 to 90 days.[4, 11] This results in the need for repeated injections and, thus, increases the treatment cost.

Method of use of botulinum toxin in trigeminal neuralgia

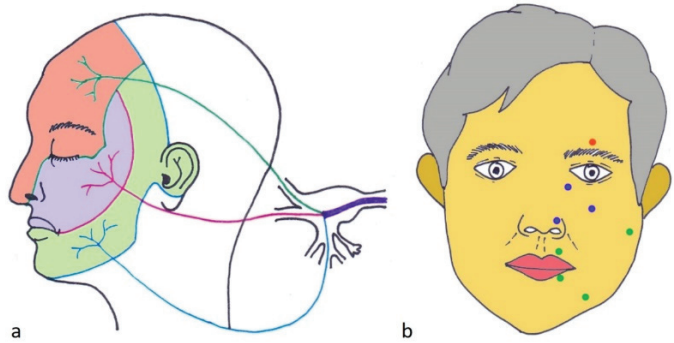

Figure6.3A: Area of distribution of pain in trigeminal neuralgia (a) and trigger zones on face according to the division of involved trigeminal nerve branches (b) [ophthalmic division (pink), maxillary division (blue) and mandibular division (green)].

A proper detailed history of the type, duration, frequency, trigger factors, and zones of pain and previous drugs should be noted prior to treatment with botulinum toxin. 100 IU botulinum toxin is diluted

with 0.9% sodium chloride solution, to yield a solution of 20–25 IU botulinum toxin per ml.

Subcutaneous and/or submucosal injections are done at the areas of pain and at the trigger zones (Figure6.3A). The dose of botulinum toxin injected depends on the extent of the pain, and reportedly varies from 20-100 IU. A total of 15-20 injection sites can be made, at an injection depth of 0.1 cm. The injection sites must be at a separation of 15 mm.

However, poor results have been noted when using subcutaneous injection for trigeminal neuralgia, when pain was confined to the gingival area. To overcome this, greater therapeutic efficacy has been seen with intra- muscular injection protocol.[4] In a study reported by Wu et al., in 2017, 50 IU of botulinum toxin was used at three separate points each in the masseter muscle on the affected side.[5] This also avoids the undesired cosmetic effects on the facial muscles and around the perioral areas following the botulinum toxin injection.

Besides subcutaneous, submucosal and intramuscular injections, direct injection into the main nerve trunks of the mandibular and maxillary divisions of the trigeminal nerve have also been successfully reported[17] (Figure 6.3B). The maxillary truck is injected by the point of entry above the zygomatic arch, midway between the external ear and the orbital rim. During insertion, the needle is pointed toward the zygomatic bone of the contralateral side, and the solution is deposited at a depth of 50mm. Injection to the mandibular root is done through the lower edge of the zygomatic arch, with the patient's mouth slightly open. The needle is inserted at the midpoint, below the zygomatic arch and proceeded until striking the pterygoid process. The needle is withdrawn slightly and the solution is deposited. For maxillary and mandibular nerve roots, 50 IU of solution is injected in each nerve root.

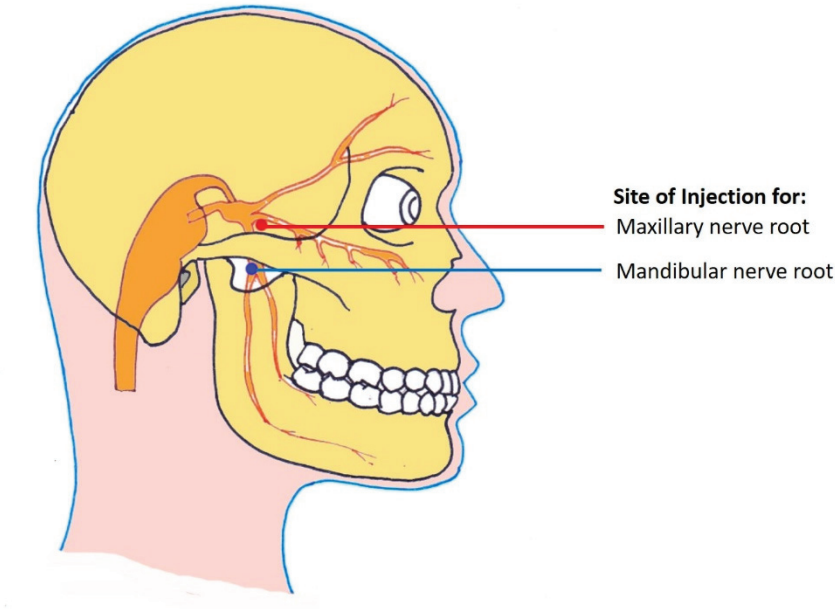

Figure 6.3B: Injection sites for the maxillary and mandibular nerve trunks.

Conclusion

Use of botulinum toxin for the control of pain in trigeminal neuralgia is a relatively novel treatment modality, which has shown promising results. Research over the past decade suggests a success rate of about 80%, with improved quality of life. The injection is made in the subcutaneous or submucosal tissue, where pain is localized by the patient. Certain authors advocate injections in the trigger zones. Injection directly into the involved mandibular or maxillary nerve root has also been reported with a high success rate. The course of treatment also suggests that further studies are needed to optimize the injection protocol for botulinum toxin in trigeminal neuralgia.

Learning points:
▪ Botulinum toxin possibly inhibits the peripheral sensitization of the nociceptive fibers. It also reduces the central sensitization by inhibiting the release of glutamate and substance P, thereby bringing about pain control in trigeminal neuralgia.
▪ Although still not very widely used, clinical research over the past decade has shown promising results, with success rates above 80%.
▪ The injections are made, subcutaneously or submucosally, in the area of the distribution of pain, as localized by the patient. Many authors have also advised injection into the trigger zones.
▪ Intramuscular injection into the masseter muscle when the mandibular branch is involved and direct injections into the maxillary and mandibular nerve roots have been reported with good results.
▪ The dose used varies from 20-100 IU, with 15-20 injection sites distributed over the areas of pain on the face.
▪ The method is relatively safe, with only mild-moderate complications of transient facial weakness and pain/swelling at the site of injection.
▪ An important limitation of its use is the temporary effect (lasting for 60-90 days), thus requiring repeated injections.

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Chapter 6.4

Botulinum Toxin in Salivary Gland Disorders

Kumar Nilesh, Monica Patil

Botulinum toxin acts on the parasympathetic nerve terminals in the salivary glands, which produces local chemical blockade and loss of neuronal activity. This leads to the inhibition of salivary flow. The toxin is clinically applied to aid in the healing of various salivary gland disorders including:

- Salivary fistulae (after sialadenectomy)[1, 2]
- Sialoceles (post traumatic and iatrogenic)[3, 4]
- Chronic sialadenitis[5]
- Sialorrhea[6]
- Auriculotemporal (Frey's syndrome) disorder. [7]

Botulinum toxin inhibits the release of presynaptic acetylcholine at the neuromuscular junctions of the salivary glands by cleaving the soluble N-ethyl-maleimide-sensitive factor attachment protein-receptors, involved in the neuroexocytosis process. This is followed by depressed parasympathetic-dependent secretory function. However, the basal flow rate is maintained by the adrenergic pathway, avoiding the risk of xerostomia. Recent biochemical studies have suggested that botulinum toxin may also modify the concentrations of salivary enzymes and solutes, such as amylases and thiocyanates.

Sialocele and Fistulas

Sialocele is defined as an accumulation of saliva in the subcutaneous tissue around the gland or duct.[8] Parotid fistula is a chronic wound of the gland, or its duct, through which saliva is discharged.[9] This may occur because of any blunt or penetrating trauma to the gland or duct, or as a complication of surgery. Parotid fistulas may also occur after temporomandibular joint surgery,

mandibular osteotomy, rhytidectomy, mastoidectomy, and dental extraction. The clinical presentations of these complications include a painless swelling around the parotid gland or duct, which may be complicated by fistula formation and infection. Although parotid sialocele and fistulas are two different entities, parotid fistula might be a progression of a sialocele.

Post-traumatic or iatrogenic sialocele and salivary fistulas are usually managed conservatively with antibiotics, pressure dressings and serial aspirations. However, these conventional management techniques involve a lengthy hospital stay, long postoperative follow-up, patient compliance and considerable discomfort, as it is very difficult to stop the salivary flow and also the resolving of these salivary disorders may take time (Figure 6.4A).

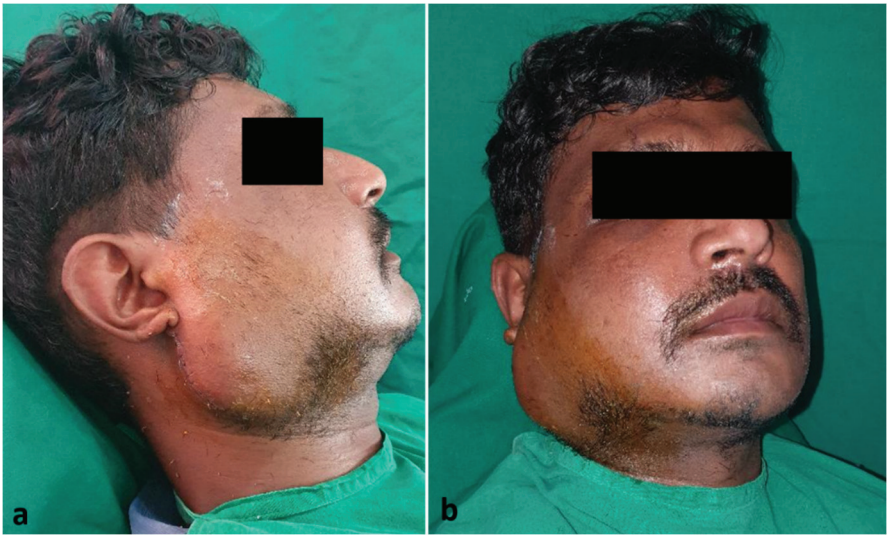

Figure 6.4A: Photographs of a patient with parotid gland sialocele in the post-operative period after the surgical management of condylar fracture

Systemic anticholinergic drugs can be used for temporary reduction in the salivary secretions, but this may be associated with side effects including dryness of the mouth, blurred vision, urine retention, photophobia, tachycardia, palpitation and anhydrosis with heat intolerance.

Traditionally, several therapies have been described in the literature for the treatment of parotid fistulae. These treatment modalities include: pressure dressing, systemic anticholinergic drugs, suction drain insertion, tympanic neurectomy (with or without chorda tympani section), surgery and the use of 2-octyl cyanoacrylate in persistent cases. However, these modalities show variable outcomes.

In order to avoid surgical management, botulinum toxin therapy can be used to obtain a temporary functional silencing of the salivary glands and to allow healing of the sialocele and/or fistula.[10] Several studies have been reported, proving a successful treatment of the salivary fistula and sialocele, either post-traumatic or post-operative, with botulinum toxin injection as the only primary therapy without pressure dressing.[11-16] Laskawi et al. reported a 90% success rate of fistula closures in a review of 12 post-parotidectomy salivary fistulae cases treated with botulinum toxin .[17]

Technique of use of botulinum toxin:

- Immediately before the injection of botulinum toxin, all cases of sialoceles should be treated with aspiration (Figure 6.4B).

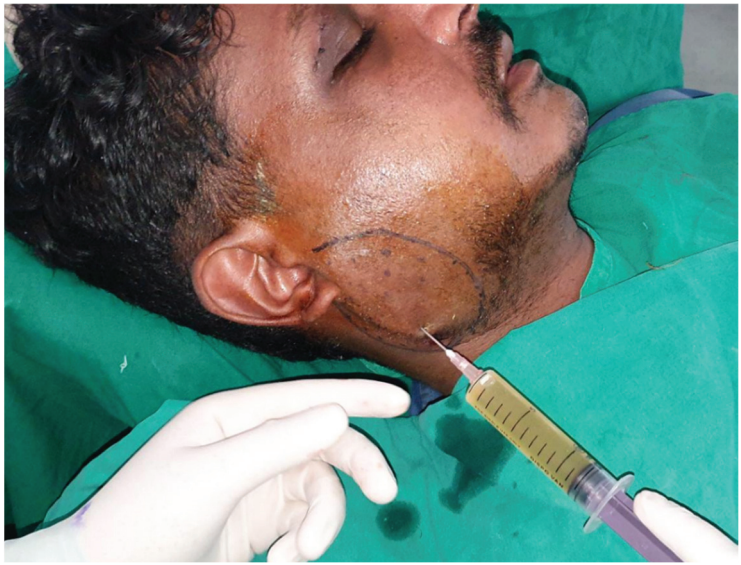

Figure 6.4B: Intraoperative photograph showing aspiration of sialocele before botulinum toxin trreatment

- Botulinum toxin is administered percutaneously. The timing of the administration varies across studies and the number of injections depends on the response to treatment. Some practitioners inject botulinum toxin as a single injection into the affected area, whereas others prefer to mark individual points (2-14 points) on the affected area and administer the toxin in divided doses among these injection points (Figure 6.4C).

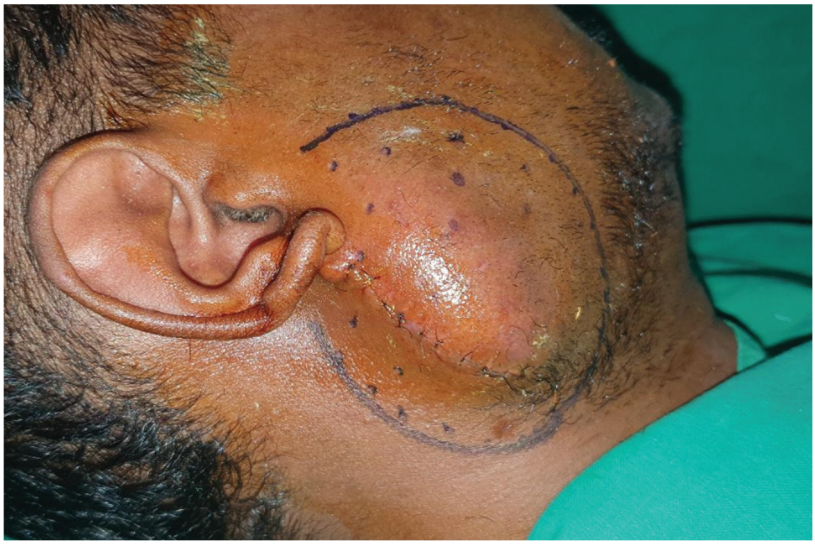

Figure 6.4C: Intraoperative photograph showing markings of injection sites over the affected parotid gland.

- Dosage of botulinum toxin ranges from 10 to 100 IU. The reported incidence of successful resolution with a single dose is around 58%.[18]

- Administration of botulinum toxin under ultrasound guidance has also been advocated by a few authors. Pressure dressings or anticholinergic medication can also be given in conjunction with the botulinum toxin treatment.

- Patients who fail to show successful results with the initial treatment can be given repeated doses of botulinum toxin. Follow-up periods with complete resolution range from 10

days to 21 months and depend on whether the patient required multiple injections and concomitant adjuvant therapy.

Saliva as a medium for dilution of botulinum toxin

Saliva can be used to reconstitute botulinum toxin-A. In 2011, after examining the medicinal and biochemical properties of saliva, Tiwari et al. stated that saliva has several beneficial properties such as an acidic pH and antimicrobial functions and contains a myriad of proteins, hormones, antibodies and other molecules.[19] To exert a biological effect, botulinum toxin requires enzymatic cleavage. In the physiological state, to cleave the proteins such as SNARE (soluble N-ethyl-maleimide-sensitive factor attachment protein receptor) proteins which are required for exocytotic release of neurotransmitters, botulinum toxin requires an acidic medium. Saliva can therefore be considered as a physiological fluid medium for dilution of botulinum toxin.

Sialadenitis

Chronic sialadenitis is a recurrent and frequently painful swelling of one or more major salivary glands, which may be characterized by episodes of acute infection. Chronic sialadenitis most commonly involves the parotid gland and radiographically presents as shot-like dilatations of the ductules and moderate dilatation of both the major and minor ducts, sometimes with stricture formation.

Promoting regeneration of the gland tissue by temporary silencing of the gland using botulinum toxin, so as to avoid gland excision in recurrent chronic sialadenitis, has been suggested.[5] Treatment with botulinum toxin in chronic sialadenitis cases due to the Stensen's duct strictures has been found to be effective in the reduction of recurrent parotitis as well as gland swelling. Recently, in studies reported by Daniel et al. in 2011[20] and O' Neil et al. in 2016[21], botulinum toxin was used in two cases of Sjögren's syndrome that were associated with recurrent parotitis, which showed a good outcome.

Technique of use of botulinum toxin:

Patients receive an intraparenchymal or perilesional injection by means of insulin syringes. The botulinum toxin is reconstituted with 0.9% sodium chloride solution (1:6 dilution) and injected preferably under color doppler ultrasonography monitoring. Following a study conducted by Capaccio et al. in 2007,[16] the parotid gland is divided

into four quadrants (the anterior, posterior, superior and inferior) and the submandibular gland is divided into two parts (the anterior and posterior) (Figure 6.4D). Each parotid gland receives 25 to 60 IU of botulinum toxin per treatment in the four quadrants, with the dose in each quadrant not exceeding more than 15 IU. The submandibular gland receives 10 to 40 IU in two divided doses not exceeding more than 20 IU, anteriorly and posteriorly. The greatest limitation in this indication is the toxin's transient effectiveness (of about three to four months), as observed in various studies, which, thus, requires multiple and expensive administrations.

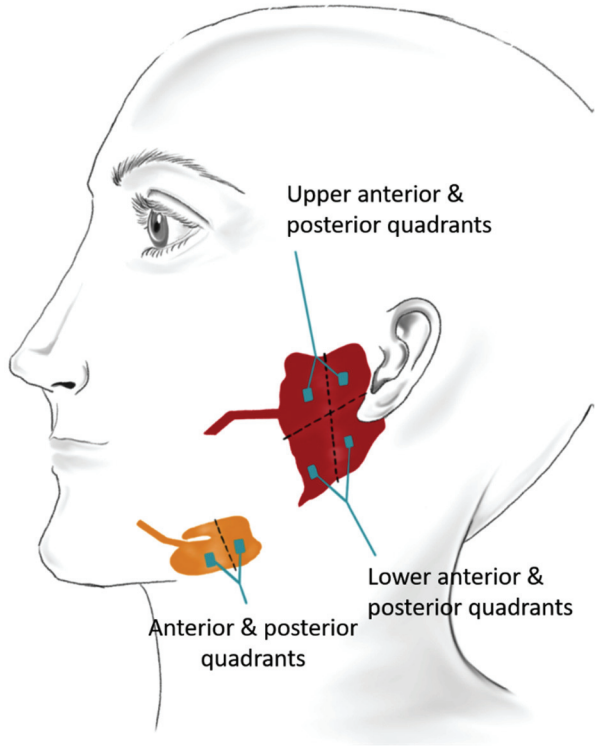

Figure 6.4D: Botulinum toxin is injected by dividing the parotid gland into the anterior, posterior, superior and inferior quadrants, while for injections in the submandibular gland it is divided into the anterior and posterior quadrants.

Frey's syndrome

Frey's syndrome is a particular condition involving gustatory hyperhidrosis of the cheek and preauricular area and is a sequela usually detected after the procedure of parotidectomy.[22] Swelling, flushing and hyperhidrosis are the common clinical symptoms of Frey's syndrome. Gustatory sweating during meal times is a characteristic feature of the syndrome. This results in a decrease in the quality of life and may have a negative impact on the social life of the affected patient.

Even after many surgical and non-surgical options were used for the treatment of Frey's syndrome, no single effective treatment was available until recently. The treatment with botulinum toxin injection in Frey's syndrome reduces hyperhidrosis and facial gustatory flushing, as described by Tugnoli et al.[23] A recent systematic review and meta-analysis by Xie et al. on the effectiveness of botulinum toxin therapy for Frey's syndrome reported an effective rate of more than 98%.[24]

Technique of use of botulinum toxin:

- Minor's test: Prior to the treatment, the involved skin area should be identified and the margins of the area involved in gustatory sweating should be marked using Minor's iodine starch test. It is an easy, clinical test to detect the skin area involved with Frey's syndrome within minutes after gustatory secretions.
- The affected skin area is then divided into fields of 1.5 × 1.5 cm using a grid template. 1 IU of botulinum toxin is injected per 1 cm.
- Treatment efficacy should be assessed at one week and four weeks after injection using Minor's test.

Conclusion

Botulinum toxin injection is an effective and safe treatment when used for functional silencing of the salivary glands in disorders such as sialoceles and salivary fistulae. It has also shown a promising role in the management of chronic sialadenitis. Botulinum toxin therapy has also been proven to be a highly successful treatment option for gustatory sweating, and can be considered as a gold

standard treatment for post-parotidectomy complications.

Learning points:

- Botulinum toxin acts on the parasympathetic nerve terminals in the salivary glands, producing a local chemical blockade, inhibiting the salivary flow. This action can be used as an aid in the healing of certain salivary gland disorders.
- Sialocele (post-traumatic or post-operative) can be treated with botulinum toxin injection, considered as the only primary therapy.
- Promoting the regeneration of gland tissue by temporary silencing of the gland using botulinum toxin has been reported. This avoids the need for gland excision in recurrent chronic sialadenitis.
- Botulinum toxin therapy has also been proven to be highly successful in the treatment for gustatory sweating and can be considered as a gold standard treatment for post-parotidectomy complications.

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Chapter 6.5

Therapeutic Applications of Botulinum Toxin in the Management of Gummy Smile

Kumar Nilesh, Monica Patil

A smile is a cornerstone of all facial expressions. It indicates pleasure, favor, amusement, approval, or sometimes scorn. A smile is not just a facial expression, but it is part of one's personality! There are two types of smile the *social* and the *enjoyment* smile. The former is voluntary, involving moderate muscle contraction, and the latter is involuntary, resulting from the maximum contraction of the lip muscles.

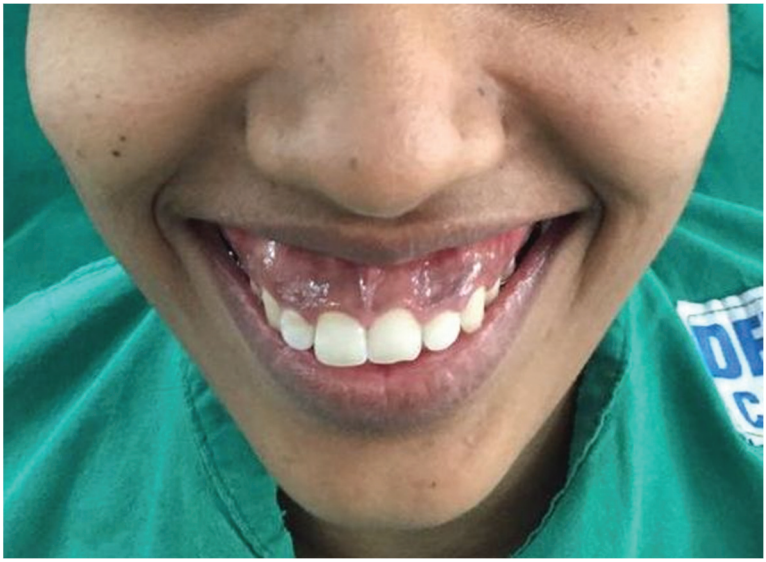

Figure 6.5A: Clinical picture showing a complete gummy smile (both anterior and posterior).

An attractive smile (also referred to as a *cosmetic smile*) is one where, on smiling, only a narrow band of 2-3 mm of the maxillary gingiva is visible. When the maxillary gingival display is greater than 3 mm, it is known as *gummy smile,* and is often considered unattractive[1] (Figure 6.5A). An anterior gummy smile is when the gingival display is more than 3 mm in the area between the canine regions, whereas a posterior gummy smile is when the gingival display is more than 3 mm in the area posterior to the canine(s).

Etiology

Every smile has three components: skeletal (contributed by the anterior maxillary skeleton) and dental (formed by the maxillary anterior teeth) which forms the two static components, whereas the elevator muscles of the upper lip form the dynamic component.

Hence, the cause of a gummy smile can also be attributed to these three factors:

- Skeletal factors
- Dental factors
- Muscular factors

Skeletal factors:

The most common cause of a gummy smile is maxillary skeletal excess.[2] It is either due to excessive vertical growth of the maxilla or the alveolar bone. This results in a discrepancy between the upper lip and the gingiva, leading to an excessive display of gingiva on smiling. A gummy smile can also be due to an anteroposterior abnormality that is localized to the maxillary central incisors along with excessive proclination of the teeth. Because of this, there is a dento-mucosal sliding of the upper lip, thus revealing a wide band of gingiva. A gummy smile due to skeletal causes can also occur due to over-eruption of the maxillary incisors and an associated dento-gingival complex. When the cause of a gummy smile is a vertical maxillary excess, the ideal treatment modality is surgery and involves Lefort I osteotomy with superior impaction.

Dental factors:

A gummy smile may sometimes be due to a delayed passive tooth eruption. Delayed passive dental eruption is due to the failure of the apical migration of gingiva, resulting in boxy/square-shaped maxillary

anterior teeth and a gummy smile. A gummy smile due to dental etiology can also be due to the abnormal size of the maxillary incisors due to para-functional habits and gingival hypertrophy/hyperplasia. In all types of the dental etiology, the amount of gingival display on smiling appears greater if the incisors are short, creating an unfavorable gum/crown ratio and excessive gingival exposure. When the cause of a gummy smile is dental, its treatment is primarily periodontal therapy and involves: gingivectomy/gingivolpasty or apically positioned flaps with or without bone resection.

Muscular factors:

The second most common cause of a gummy smile is the hyperactivity of the upper lip muscle. Hyperactivity of the muscles that are responsible for smiling and, in turn, elevating the upper lip i.e., the levator labii superioris alaquae nasi, the levator labii superioris and the zygomaticus major and minor contributes to the occurrence of a gummy smile[2] (Figure 6.5B). The gingival show is more in patients having an anatomically short upper lip.

The hyperactivity of the upper lip muscles can traditionally be managed with various techniques, including vestibular mucosa resection, myotomy with partial resection of the levator muscles, and subperiosteal dissection of the lip-elevating musculature. The above-mentioned surgical procedures conventionally used to treat a gummy smile are irreversible and invasive. However, the use of botulinum toxin for management of a gummy smile is relatively safe, reliable, and reproducible. Table 6.5A enlists the causes of a gummy smile and its treatment.

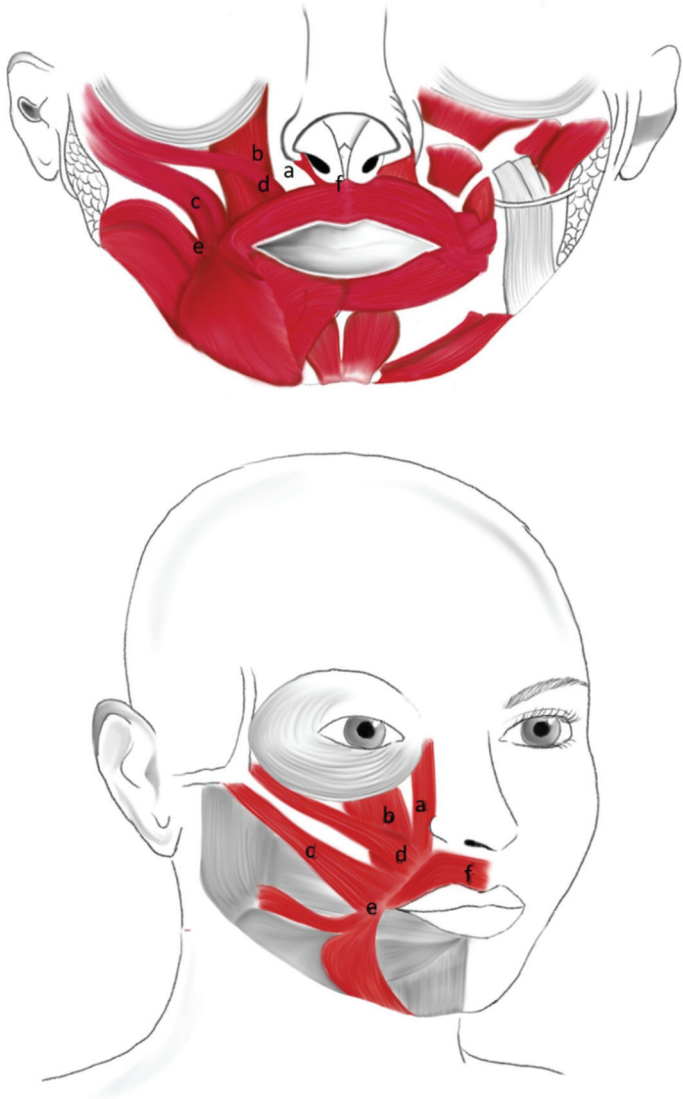

Figure 6.5B: Hyperactivity of the muscles of the upper lip; namely (a) the levator labii superioris alaquae nasi, (b) the levator labii superioris, (c) the zygomaticus major, (d) the zygomaticus minor, (e) the risorius, and (f) the depressor septi nasi leads to a gummy smile

Treatment options for a gummy smile

A wide range of treatment modalities have been described in the literature for management of a gummy smile. Both surgical as well as non-surgical methods have been used for the correction of a gummy smile based on its etiology (Table 6.5A).

Table 6.5A: Components, cause and management of a gummy smile

Component	**Skeletal**	**Dental**	**Muscular**
Cause	Vertical maxillary excess	Delayed passive eruption	Upper lip elevator muscles hyperactivity
Cure	▪ Lefort I osteotomy with superior maxillary Impaction	▪ Gingivectomy ▪ Gingivoplasty ▪ Apically positioned flaps with or without osseous surgery	▪ Vestibular mucosal resection ▪ Levator muscle(s) myotomy or myectomy ▪ Botox

However, a novel, minimally invasive technique for the management of a gummy smile using botulinum toxin has gained popularity in recent years. The first reported use of botulinum toxin for the management of a gummy smile was published by Dr. Mario Polo in a pilot study in 2005.[2] Since then, multiple case reports and some prospective studies on the use of botulinum toxin injection for treatment of a gingival smile have showed promising results.[1-5] Though it has not gained United States-FDA approval for this indication, botulinum toxin is currently often used to treat excessive gingival display as an off-label procedure in the US and other parts of the world.

Technique of using botulinum toxin in the treatment of a gummy smile:

For use of botulinum toxin in the treatment of a gummy smile, certain factors need to be compared, including:

1. Which patients should be selected for the treatment (Indications)
2. Which are the muscles to be injected?
3. What is the preferred dose of injection for the treatment?

Indications

Any patient with a gummy smile (a gingival show of more than 3 mm) caused due to the hyperactivity of the levator muscles of the upper lip are candidates for botulinum toxin therapy. However, it is prudent to select patients with a gingival display of 5 mm or more. When used in patients with a gingival display of 3-5 mm, it usually results in a negative gingival display (a smile line on the incisal surface of the incisors), which is often perceived as unaesthetic.

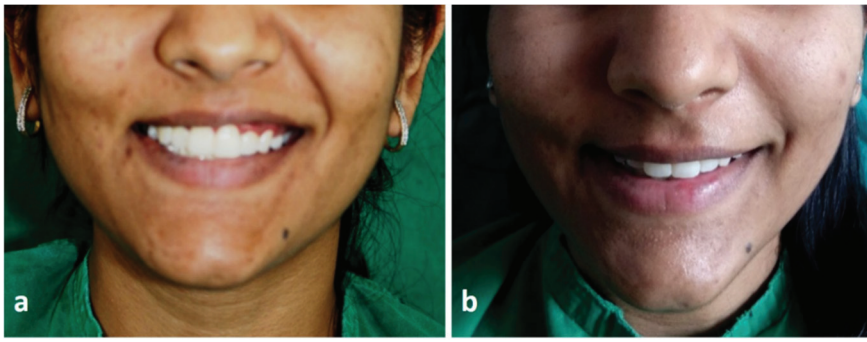

Figure 6.5C: Use of botulinum toxin in a patient with minimal unilateral (left) gummy smile, treated with toxin therapy, leading to an unaesthetic negative gingival display

Although a gummy smile due to the other causes (skeletal or dental) required surgery for a more definitive management, botulinum toxin is indicated in patients who do not want surgical intervention or as an interim measure before the surgery is undertaken. It can also be used to supplement the surgical procedure for management of a gummy smile.

Technique, dose and sites of injection:

- Diagnosis of a gummy smile should be done by a series of clinical and photographic parameters.
- The injection points should be determined according to the type of gummy smile (anterior or posterior).
- By asking the patient to smile, the injection points should be marked by muscle animation.
- For an ***anterior gummy smile***, the muscles injected are: the levator labi superioris alaquae nasi and the levator labi superioris (Figure 6.5C).
- For the levator labi superioris alaquae nasi, the injection point is marked 2-3 mm lateral to the ala of the nose. After marking the injection point, 2.5 IU of reconstituted botulinum toxin-A is injected at this point.
- For the levator labii superioris, the injection point is marked at the junction of the upper 1/3rd and lower 2/3rd of the naso-labial fold. After marking the points, 2.5 IU of reconstituted botulinum toxin-A is injected at this point.

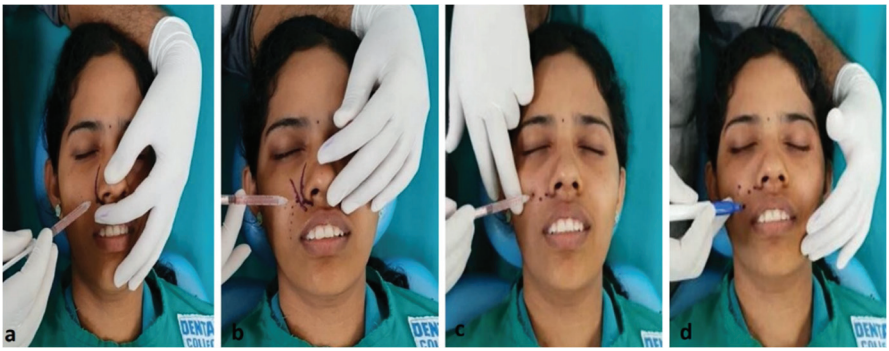

Figure 6.5C: Intraoperative photograph showing injection sites for the management of an anterior gummy smile for LLSAN(a), LLS(b), ZM-ZMn at its origin (c) and insertion (d)

- For a ***posterior gummy smile***, the muscles injected are the zygomaticus major and the zygomaticus minor (Figure 6.5D

(b)).

- The origin of the zygomaticus major and minor is determined by asking the patient to smile and the point of the highest prominence of the soft tissue cheek is the point of injection. The point of injection, whether 1-point or 2-points, is determined by the gingival exposure. If the gingival exposure is less than 7 mm then a 1-point injection is sufficient and if the gingival exposure is more than 7mm then a 2-points injection is advisable.

- The muscles injected and the anatomical landmarks are highlighted in Figure 6.5D and Table 6.5B.

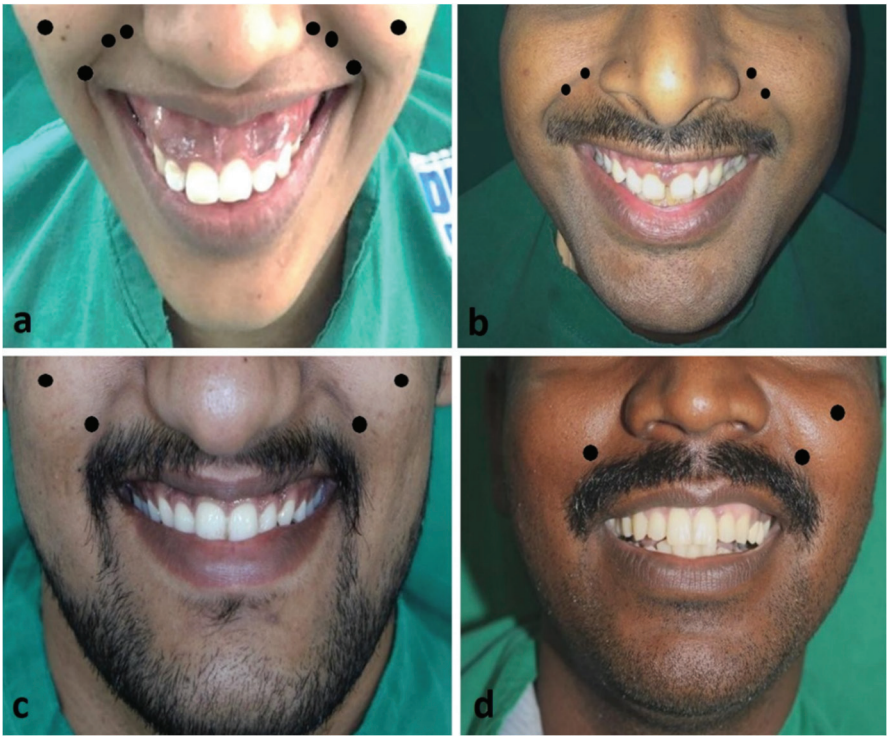

Figure 6.5D: Injection points for mixed (a), anterior (b), posterior (c) and asymmetric (d) gummy smile.

Table 6.5B: Site and landmarks for injection		
Type	**Muscle Injected**	**Area/Landmark**
Anterior Gingival Smile	LLSAN	3-5 mm lateral to the ala of the nose
	LLS	Junction of the upper 1/3rd and lower 2/3rd of the nasolabial fold
Posterior Gingival Smile	Z-major & Z-minor Inferiorly	Most lateral portion of the naslolabial fold on smiling
	Z-major & Z-minor Superiorly	Point of prominence of the cheek or 2 cm lateral to the 1st point and in line with the tragus

- **Dose:** The dose of botulinum toxin-A is determined by the severity of gingival display, type of gummy smile and number of injection points.[6] It is always advisable to start initially with lower doses. The gingival display of more than 3 mm may require only 2 IU of BTX-A whereas a gingival display of more than 5 mm may require 7.5 IU of botulinum on either side.[2, 5, 7] The results of the management of various types of gummy smile with botulinum toxin are presented in the clinical photographs (Figures 6.5E to 6.5H).

The effect of BTX-A starts by the 1st to 3rd day after injection and is perceived by the patient, as the smile appears different. The effect is at maximum after two weeks and then gradually decreases over the next six months. There are individual variations and the duration of action depends upon the dose, the number of muscles injected, previous injections, and the age of the patient. The duration of effect of botulinum toxin is longer in patients who receive repeated doses.

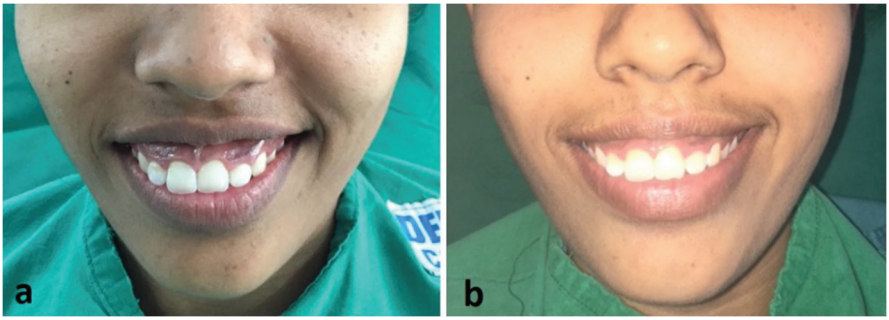

Figure 6.5E: A case of mixed gummy smile. The anterior gingival display was 10 mm and the posterior gingival display was 6 mm (a) and (post-operative result at two weeks' follow-up (b).

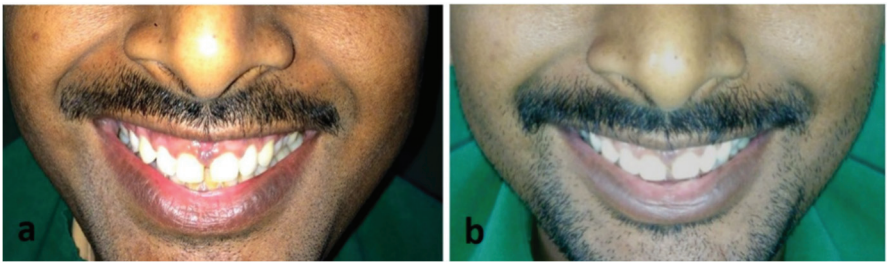

Figure 6.5F: A case of anterior gummy smile with gingival display *of 5 mm (a), post-operative result at two weeks' follow-up (b).*

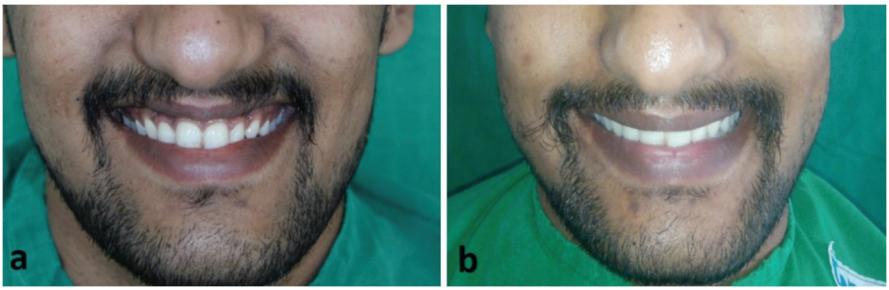

Figure 6.5G: A case of posterior gummy smile with gingival display of 4 mm (a), post-operative result at two weeks' follow-up (b).

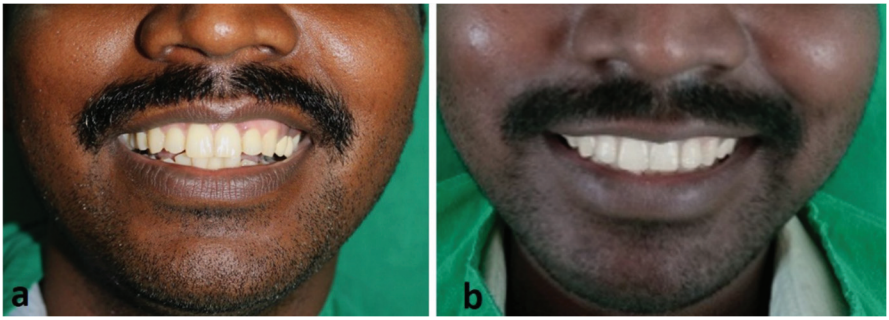

Figure 6.5H: A case of asymmetric gummy smile with gingival display of 5mm on left side (a), post-operative result at two weeks' follow-up (b).

Complications:

Complications of this procedure are rare and mostly attributed to the faulty injection technique. The possible complications include:

- Injections that are placed too close to the mouth or within the orbicularis oris muscle which can cause flaccid cheek, incompetent mouth, or an asymmetric smile.
- Unequal doses, or asymmetric sites, of the injection may result in an asymmetric smile.
- Other adverse effects, including drooling of saliva, and difficulty in speaking and eating are rare and may result from gross errors in the injection procedure.
- Higher doses injected into the insertion points of the muscle may lead to a collapse of the oral commissure giving a sad appearance.

Most of these adverse events are transient and can easily be corrected with retouching at the follow-up visit.

Conclusion

Management of the gummy smile using botulinum toxin is an effective but transient method. The patients should be selected carefully and the dose and site of injection depend upon the degree

of excessive gingival exposure. The adverse effects of botulinum toxin are rare and, likewise, are transient and easily corrected with altered doses.

Learning points:
➢ When the maxillary gingival display is greater than 3 mm, it is known as a gummy smile.
➢ Hyperactivity of the muscles that are responsible for smiling (the levator labii superioris alaquae nasi, the levator labii superioris and the zygomaticus major and minor) and, in turn, elevating the upper lip contributes to the occurrence of a gummy smile.
➢ The dose of botulinum toxin-A is determined by the severity of the gingival display.
➢ For an anterior gummy smile, the muscles injected are: the levator labii superioris alaquae nasi and the levator labii superioris.
➢ For a posterior gummy smile, the muscles injected are: the zygomaticus major and zygomaticus minor.

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Chapter 6.6

Use of Botulinum Toxin in Wound Healing

Monica Patil, Kumar Nilesh, Eesha Pisal

Introduction

Wound healing is a complex and well-sequenced process of the cellular and biochemical responses. The process of wound healing works toward restoring the tissue integrity and functional capacity following an injury. It is affected by a variety of intrinsic and extrinsic factors.

The healing response differs primarily on the type of tissue involved, the nature of the tissue disruption, and the wound closure. Healing by first intention occurs when a clean laceration or surgical incision is primarily closed with sutures or by other means and healing proceeds rapidly with no dehiscence and a minimal scar formation (Figure 6.6A (a)). Whereas, healing with secondary intention is complicated and occurs through granulation and connective tissue formation. It is commonly seen in avulsed injuries, local infections or an inadequate closure of the wound, that, in turn, forms wide scars (Figure 6.6A (b)).

Widening of the scars result in an unaesthetic appearance. Poorly healed facial scars are not only unaesthetic, but also have a negative socio-psychological impact. This is one of the most common reasons why people seek emergency medical care for facial laceration for aesthetic concern as well as to receive the best cosmetic outcome.

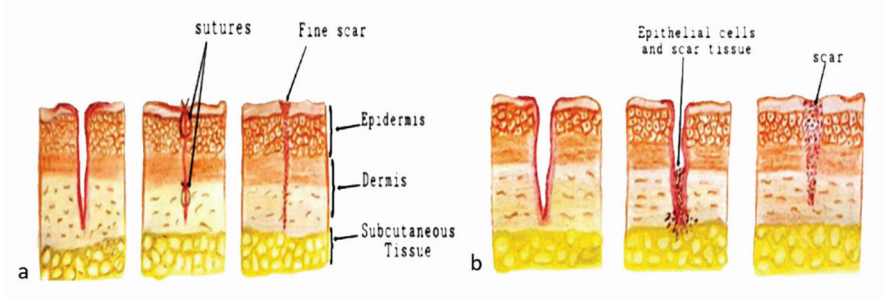

Figure 6.6A: Diagrammatic representation showing wound healing by primary (a) and secondary intention (b).

Influence of the underlying musculature on wound healing

The occurrence of scar widening is seen more on the face than on any other parts of the body, as the face has abundant musculature. A widening of the scars is mainly a result of the mechanical forces created by these muscles, like the tensile distracting forces, the elastic forces of the adjacent skin, and external pressure.[1] These forces act on the resilient, immature collagen, which pulls the wound edges in multiple directions.[2] This concept is confirmed by the outcome of the healing wounds relative to the lines of Langer (Figure 6.6B).

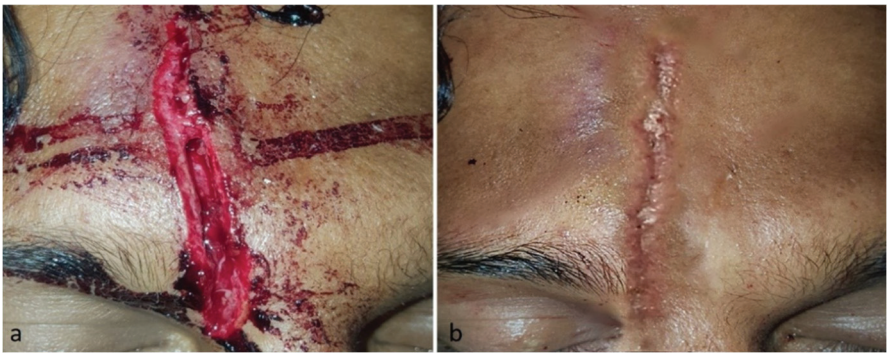

Figure 6.6B: Photograph showing traumatic forehead laceration (a) and widening and scarring of the wound post healing (b).

These lines of Langer lie perpendicular to the tension vector of the underlying muscular contraction. Thus, the scars aligned with the

lines of Langer are subjected to relatively less tension and, thus, heal well. Whereas, scars oriented against them are subject to repetitive tension, resulting in scar widening.[1] A key factor which determines the final cosmetic outcome of a cutaneous scar is the tension that acts on the wound edges during the healing phase.[3] It is believed that the continuous muscle activity of the skin around the wound causes repeated microtrauma and induces a prolonged inflammatory response and increased metabolic activity during the healing process. This intensifies the hypertrophic and hyperpigmented scars by the extracellular deposition of collagen and glycosaminoglycans.

One way to reduce the deleterious effects of the dynamic tension caused by the local muscle pull is to temporarily denervate the muscles that pull the wound edges apart through chemo-immobilization using botulinum toxin.

Application of botulinum toxin in wound healing

There are various studies that have focused on the treatment rather than the prevention of unexpected surgical scars. Similarly, a variety of guidelines and approaches has been recommended in the literature to reduce or avoid wide scars. Surgical manoeuvres to reduce the tension on the healing wounds that involved the creation of flaps that were buried under the skin and used to bear the tension on the healing wound were described by Millard.[4] Another popular treatment method uses corticosteroid injections. However, the outcome consists of thin, atrophic, telangiectatic, erythematous skin, which makes clinicians reluctant to use them.[5]

Early management of surgical scars is more likely to yield a better cosmetic appearance and avoid the requirement for re-treatment.[6] Various techniques, such as undermining of the skin, layered closure, and use of adhesive tapes reduce the muscle tension acting on the healing wound, but do not completely eliminate it.

The application of botulinum toxin in the reduction of facial scars was first reported as a trial on primates by Gassner et al. in 2002.[7] The forehead was chosen as the excision site and the experimental and control excisions were each planned in symmetric anatomic locations in the same individual animal. The experimental side was injected with botulinum toxin and the control side was injected with 0.9% normal saline after suturing. Botulinum toxin proved to be efficient in improving the scar appearance.

Wilson (2006)[4] studied 40 patients with scars on the face (both post-trauma and post-surgery). Botulinum toxin was used to induce temporary paralysis of the muscles during revision surgery (immediately after suturing), thus minimizing the tension on the healing wound edges until the collagen could mature. Using both objective and subjective assessment scales, 90% of the patients showed an improved outcome.

The neurotoxin acts by inducing chemo-denervation through its action on the presynaptic neuron and prevents the release of acetylcholine, which leads to the functional denervation of the striated muscle for two to six months after injection.[8] This results in muscle weakness and subsequent clinical flaccid paralysis. Temporary paralysis of the facial muscles underlying the wound is expected to give the crucial advantage of providing rest during wound healing until the collagen matures. This reduces the tensional forces that pull the suture line, resulting in wide scars.

One of the limitations of using botulinum toxin can be the delay in the onset of its action, which may warrant additional injections during follow-up for complete paralysis around the wound. To overcome this, Gassner et al. (2000) performed a study to determine the paralyzing effect of botulinum toxin type-A reconstituted in a solution of lidocaine with epinephrine (BTX with 1% lidocaine with 1:100,000 epinephrine. With this reformulation, paralysis is observed within 5 to 10 minutes after injection. When compared with pure botulinum toxin injections, this formulation is also reported to be a safer alternative with superior pharmacological properties. The simultaneous injection of botulinum toxin and a local anaesthetic with vasoconstrictor reduces its local diffusion and provide the physician with immediate feedback on the desired treatment effect.[9] Additionally, the anaesthetic agent, lidocaine stabilizes the neuronal membrane and inhibits the ionic fluxes that are required for initiating and conducting the neuronal impulses. This mechanism provides an immediate muscle paralysis by blocking the efferent fibers.

Technique of use of botulinum toxin:

- The botulinum toxin injection is used prior to the suturing of the lacerations. It is important to subject every patient to an allergy skin test for BTX-A.

- The lacerations to be treated should be cleaned and debridement of the wound and the surrounding skin should be prepared using standard aseptic procedures.
- After the aseptic procedure, botulinum toxin is prepared for injection. Two methods of reconstitution of botulinum toxin to advocate are:

  1) In the normal formulation, one vial of botulinum toxin (100 IU) is diluted in 5 ml of normal saline solution to attain a concentration of 20 IU/ml)

  2) Another way of reconstitution includes the use of a local anaesthetic agent. One vial of botulinum toxin (100 IU) is diluted in 10 ml of 0.9% injectable saline and 3 ml of solution of 2% lidocaine with 1: 200,000 epinephrine.

- The botulinum toxin is then injected adjacent to the wound, along the length of the laceration (1.5 IU per cm of the wound length), with the needle prick placed approximately 3-4mm from the edge of the wound and to the depth of the expected facial musculature around the specific anatomic site of the wound (approximately 5-8 mm) (Figure 6.6C).

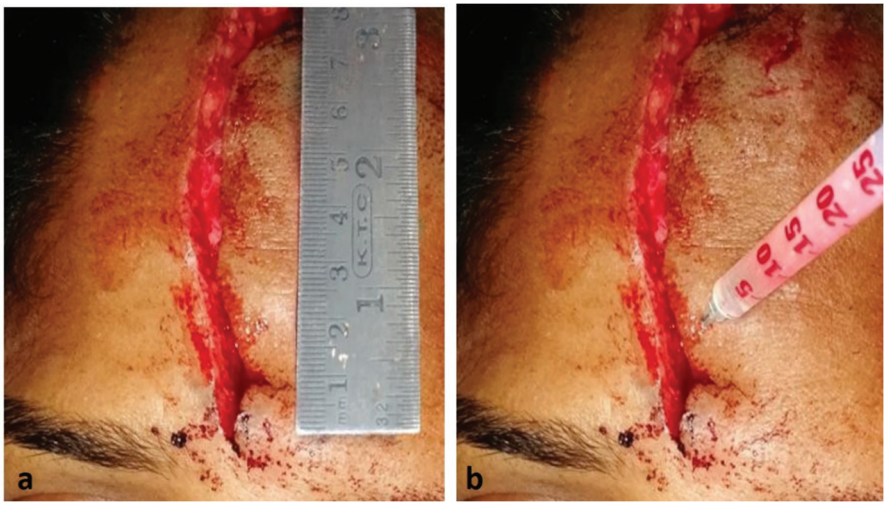

Figure 6.6C: Injection of botulinum toxin adjacent to the laceration (a) suturing of the laceration (b).

- The laceration is then repaired in layers after the injection procedure is completed. The laceration is sutured in layers with vicryl 4-0 for the subcutaneous layer and ethilon 5-0 for the cutaneous layer (Figure 6.6D).

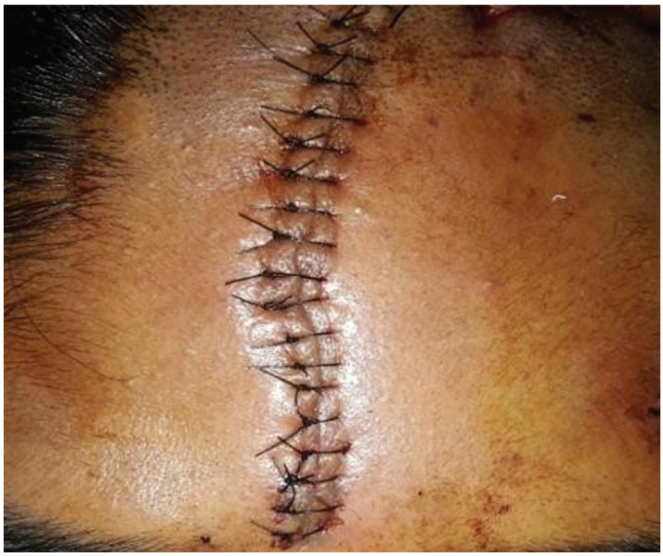

Figure 6.6D: Layered closure of laceration.

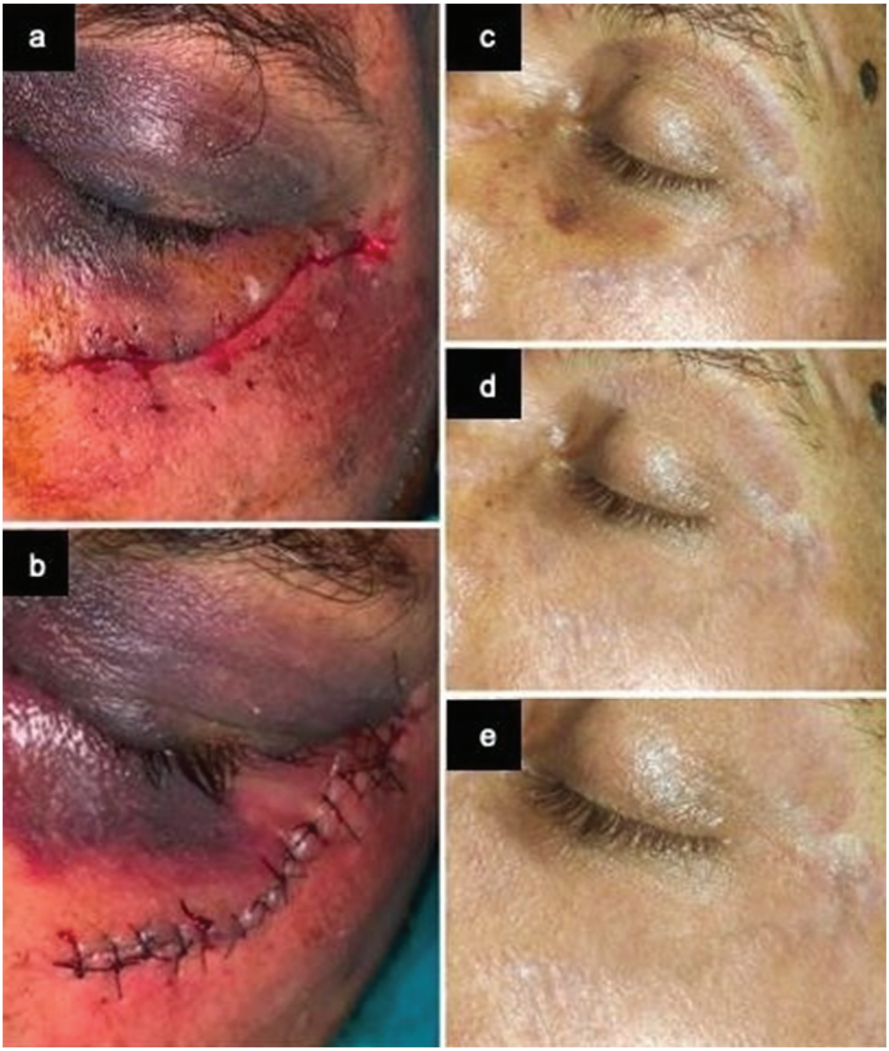

Figure 6.6E: Photographs showing: (a) a laceration over the right frontal bone treated with BTX-A, (b) a sutured laceration, (c) a scar at one week follow-up after suture removal, (d) minimal scarring seen at three months' follow-up, and (e) complete wound healing with good appearance at six-months' follow-up.

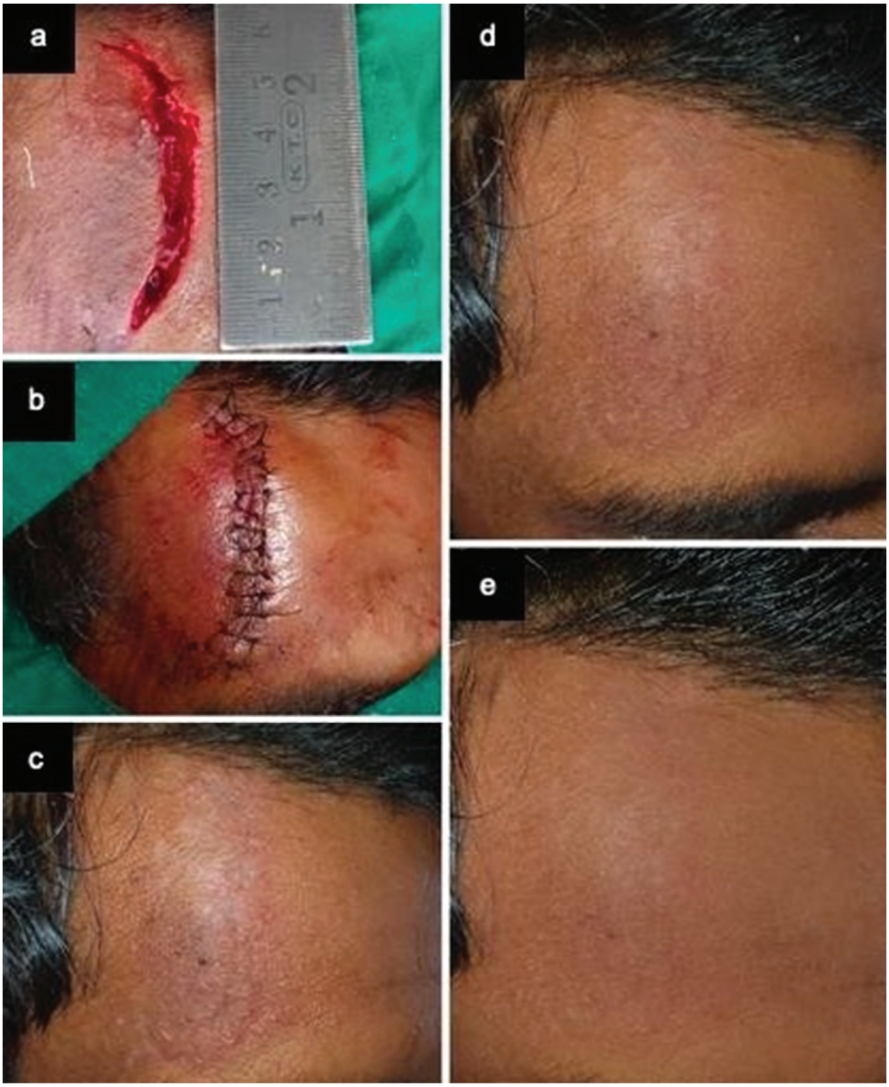

Figure 6.6F: Photographs showing: (a) a laceration over the frontal bone treated without BTX-A, (b) a sutured laceration, (c) a scar at one week of follow-up after suture removal, (d) uneven scarring seen at three months of follow-up, and (e) complete wound healing showing visible scars at six-months of follow-up.

Conclusion

Botulinum toxin injections for wound healing cause a chemo-immobilisation of the muscles. This reduces the tensile forces which act on the suture line and cause wide scars. This, in turn, improves the appearance of facial wounds after trauma as well as in cases of scar revisions, with minimal scarring (Figure 6.6E, F).

Learning points:
▪ A widening of the scars results when opposing forces acting on the newly formed collagen pull the suture line apart before the final maturation of the healing lacerations.
▪ These undesirable forces can be eliminated by the paralysis of the facial muscles surrounding the lacerations, by injection of botulinum toxin.
▪ Chemo-immobilisation caused due to injections of botulinum toxin lead to an improvement in the appearance of facial wounds after trauma as well as in cases of scar revisions.
▪ The simultaneous injection of botulinum toxin and a local anaesthetic with vasoconstrictor reduces its local diffusion and provides the physician with an immediate feedback on the desired treatment effect.

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Chapter 6.7

Botulinum Toxin for the Management of a Condylar Fracture

Kumar Nilesh, Monica Patil

Introduction

In the field of maxillofacial trauma, the management of condylar fracture in adults has generated more discussion and controversy than the fracture of any other facial skeleton. The options for the management of condylar fractures vary from conservative management with intermaxillary fixation followed by physiotherapy to the open reduction and internal fixation of the fracture.

Mandibular condylar fractures are common and account for about 25-35% of all types of mandibular fractures.[1] Even after an elaborate review of the literature for the absolute and relative indications for open reduction of mandibular condylar fractures, there has still been no definitive study which demonstrated the superiority of closed versus open reduction, or vice-versa.[2] There are various factors which need to be considered in choosing a particular treatment option including: the age of the patient, the surgical expertise of the surgeon in open reduction of the complex temporomandibular joint area, assessment of the risk of damage to the vital structures, the degree of fracture displacement, and the derangement of occlusion.

One of the most critical factors influencing the choice of treatment and a successful outcome in the management of a condylar fracture is the degree of displacement of the fractured segments. While it is widely accepted that severely displaced fractures are best managed by open reduction for proper alignment of the fracture segments, the minimally displaced or undisplaced fractures can be managed by closed reduction with intermaxillary fixation. When either open or closed reduction is undertaken it is essential to understand and minimize the displacing forces acting on the fractured condyle for better anatomical reduction and primary fracture healing.

Influence of the masticatory muscles on a condyle fracture

It is believed that there are two major forces that cause the displacement of the fractured condylar segment:

1. Traumatic force that leads to the fracture of the bone and
2. Muscular force (i.e., the masticatory muscle contractions).

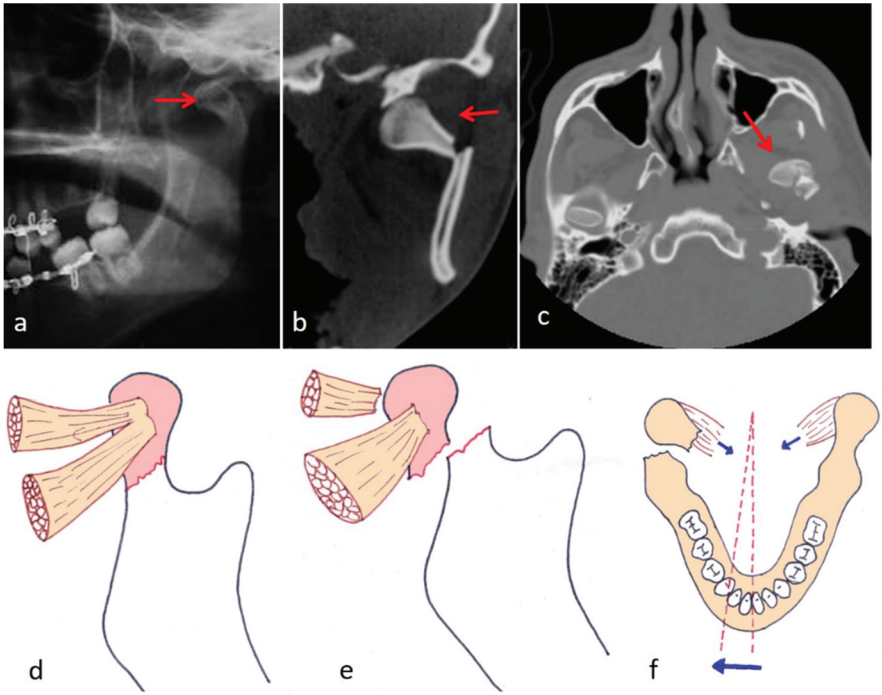

Figure 6.7A: Imaging findings of a fractured condyle showing displacement in the anterior and medial direction on an orthopantomogram (a) and on the coronal (b) and the axial section (c) of the computed tomography. Line diagrams showing the attachment of the lateral pterygoid muscle on the condyle neck (d), and the role of the inferior head of the muscle in a fracture dislocation (e, f).

Among the four primary muscles of mastication, the lateral pterygoid muscle plays the most significant role in the displacement of the condyle fracture (Figure 6.8A (a, b, c)) The lateral pterygoid has two

heads: the superior head originates from the greater wing of the sphenoid bone and inserts into the articular disc, whereas the inferior head originates from the lateral surface of the lateral pterygoid plate and inserts into the anterior surface of the neck of the condyle (called the pterygoid fovea). This insertion of the inferior head has an important role in the displacement of the fractured condyle (Figure 6.8A (d)). The pull of the inferior head of the lateral pterygoid displaces the fractured condyle in the anterior and medial direction (Figure 6.8A (e, f)).

Besides the primary role of lateral pterygoid muscle in the displacement of the fractured condyle, the temporalis, the medial pterygoid and the masseter muscle together cause a superior displacement of the ramus segment. This results in the telescoping of the mandibular ramus towards the glenoid fossa, with a resultant shortening of the ramal height, the ipsilateral gagging of occlusion, and a deviation of the chin to the affected side (Figure 6.8B).

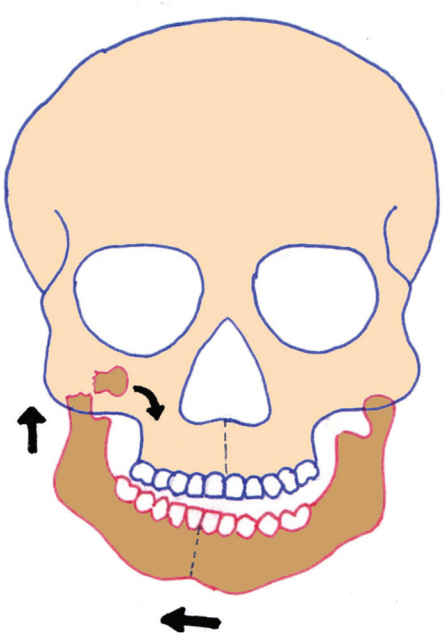

Figure 6.7B: Photograph showing a unilateral condyle fracture causing a deviation of the face to the affected side and an overriding of the ramus superiorly.

Application of botulinum toxin in management of condyle fracture:

Even when traumatic forces do not cause a displacement of the fractured condyle, the masticatory muscle's contraction may still cause its displacement. The horizontal displacement of the condyle is caused by the lateral pterygoid muscles, while the superior telescopic overriding of the ramus over the condyle is due to the contraction of the pterygo-masseteric unit (the medial pterygoid and masseter) and the temporalis muscle. Therefore, it is beneficial to overcome the forces of these muscles for the adequate reduction of the displaced fracture segments as well as to keep it in the reduced position during fracture healing. Botulinum toxin can be used to cause the transient paralysis of these muscles. This will weaken the muscle forces, thus, aiding in the better reduction and adaptation of the fracture ends. The elimination of the excessive muscle forces will also help in the undisturbed bone healing, thus, resulting in the union of the fractured segments.

Although the use of botulinum toxin appears to be beneficial, it has not yet been very widely reported in the literature. One of the limitations can be the cost of the toxin and a possible lack of awareness, as well as the need for training in the administration of the drug among treating surgeons. Besides sporadic case reports, only two scientific papers have been published on the successful use of the toxin in the management of a condyle fracture.[3, 4] A summary of both studies is presented in Table 6.7A.

Author and Year	Demographic details and fracture type	Treatment	Muscle Injected	Total Dose
Canter et al., 2006[3]	3 to 51 years (n=10) Male: Female =6:4 Minimally displaced unilateral condylar fracture	Closed reduction	Transcutaneous injections into the masseter and the temporalis (30 IU each), Transmucosal injections into the medial and lateral pterygoid (40 IU)	100 IU

Al-Mahmoudy et al., 2019[4]	**7 to 44 years (n=10)** **Male: Female = 8:2** **Both uni- and bilateral condylar fracture**	**Open reduction**	**Ultrasound guided transcutaneous injection of toxin into the lateral pterygoid muscle.**	**10-20 IU**

Technique for use of botulinum toxin:

- The botulinum toxin injection is used as an adjunct in the management of a condyle fracture. It can be used either with the open or closed method of fracture treatment. It can be used in cases of both unilateral and bilateral condyle fractures (for a fracture at the condyle neck and a subcondylar fracture).
- When closed treatment is used, a fracture without severe angulation or deviation of the condylar head (but with an overriding of the fracture segments) should be the choice of application for the adjuvant toxin therapy.
- The muscle(s) to be injected is variable, depending on the extent of paralysis desired. While the lateral pterygoid (the inferior head) is the main muscle to be treated, additional injections into the masseter, the anterior fiber of temporalis and the medial pterygoid can be made when desired (a significant telescoping of the ramus segment with a reduced ramal height).
- One vial of botulinum toxin (100 IU) is diluted in 5 ml of normal saline solution to attain a concentration of 20 IU/ml. A 26-gauge one and half inch-long needle is used for the injection.
- Botulinum toxin is injected into the masseter and the anterior fibers of the temporalis muscles (30 IU each) through the percutaneous extraoral route (Figure 6.8C). The posterior fibers of the temporalis are not treated, so as to preserve the physiological neuromuscular adaptive mechanism. A minimum depth of 1 cm should be spared during injection through the percutaneous extraoral route to spare the

superficial muscles of the facial expression. While treating patients with traumatic injuries to the face, caution should be taken, considering the already injured soft tissues, the presence of facial edema (thereby requiring a greater depth of transcutaneous injection to reach the underlying muscle), and pain on palpation of the injection landmarks and mobile underlying bone segments.

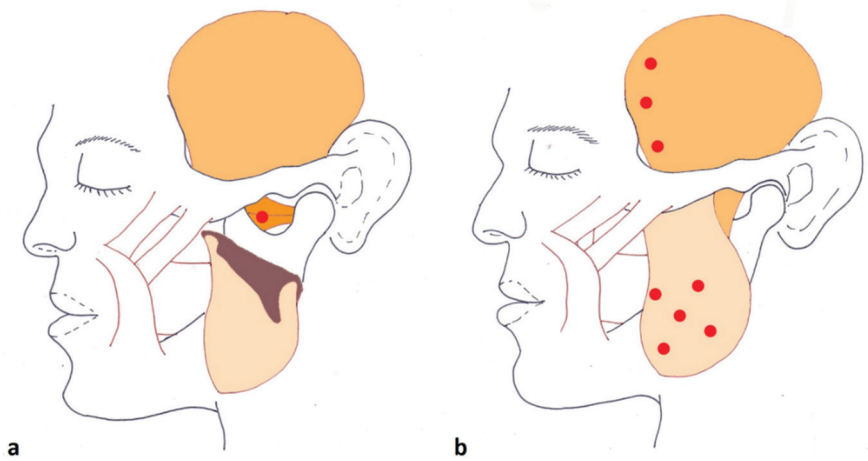

Figure 6.7C: Sketches showing areas of injection for the lateral pterygoid muscle (a) and the masseter and temporalis muscles (b).

- The medial and lateral pterygoid muscles are paralyzed by injecting an additional 40 IU of the toxin either through the transmucosal intraoral route or the transcutaneous extraoral route. Unlike the externally located masseter and temporalis muscles, injections into the lateral and medial pterygoid are more difficult, requiring an increased depth of needle insertion, knowledge of the vital anatomical structures and a greater risk of complications including bleeding and hematoma.

Botulinum toxin injection in the lateral pterygoid muscle:

The access to the lateral pterygoid muscle can be performed intraorally or extraorally. Both approaches are complicated in comparison to injections into the superficial muscle fibers of the masseter and the temporalis. Very often, ultrasound or electromyographic guidance is required to ensure a successful intramuscular injection, and to

reduce the risk of any untoward complications.

Intraoral transmucosal method:

The patient is placed in a semi supine position with the mouth partially open (about 20 mm). The needle is inserted above the mucobuccal fold of the maxillary second molar tooth, and moved in an upward and inward direction keeping it close to the maxillary tuberosity until the needle tip hits the pterygoid plate, so as to deposit the solution into the inferior head of the pterygoid (Figure 6.8D).

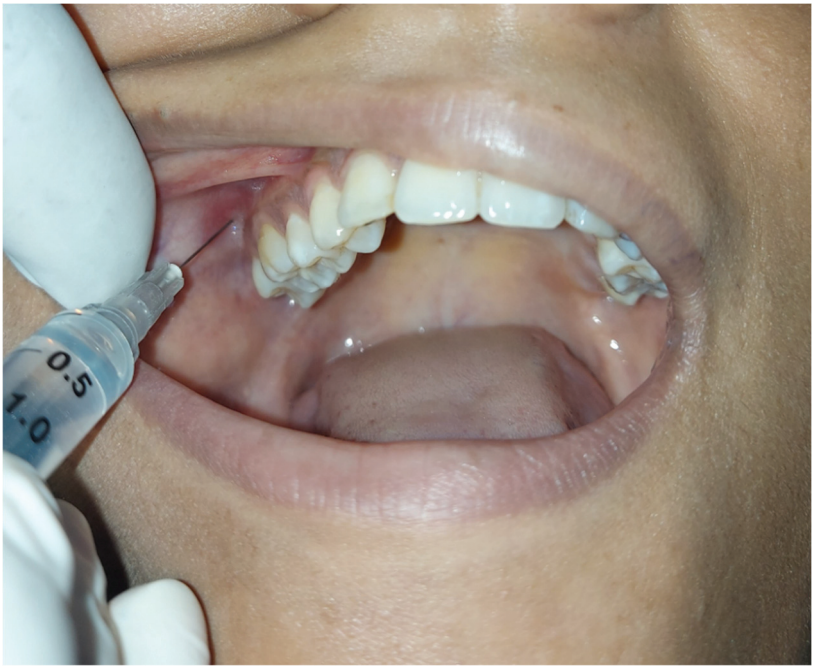

Figure 6.7D: Intraoral injection into the lateral pterygoid muscle.

Extraoral transcutaneous method:

The extraoral technique requires a detailed anatomical knowledge of the pterygoid muscle located in the infratemporal fossa. For the injection, the patient is placed in a supine or semi supine position, with the jaw partially open. The operator then palpates the zygomatic arch above and the condyle behind. The injection area is located

below the arch and in front of the condyle. The area of injection is into the sigmoid notch, bounded superiorly by the zygomatic arch, anteriorly by the coronoid process and posteriorly by the condyle of the mandible. Once the landmarks are palpated extraorally, the needle is inserted into the skin and then passes through the fibers of the the masseter and temporalis muscles. The needle must penetrate about 30-40 mm through the masseter muscle and the temporalis tendon before it reaches the inferior head of the lateral pterygoid. According to some authors, the point of entry of the needle is 35 mm from the external auditory canal (i.e., anterior to the mandibular condyle) and 10 mm from the lower border of the zygomatic arch. The needle is angled 15° upward and is directed toward the roots of the upper 3rd molars to reach the inferior head of the lateral pterygoid muscle and the solution is deposited.

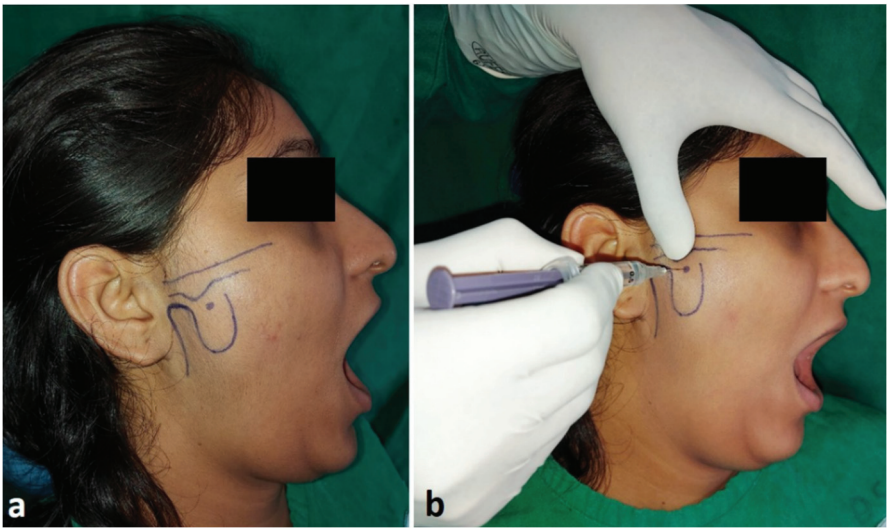

Figure 6.7E: Extraoral injection landmarks (a) and injection into the lateral pterygoid muscle.

- The injection should preferably be given two to three days prior to the planned procedure of intermaxillary fixation or open reduction of the fracture, as the effect of the toxin begins within 24 hours and attains its peak within a week.
- The use of botulinum toxin helps in inhibiting strong muscle contraction. It weakens the pull of the lateral pterygoid muscle,

thus, aiding in the reduction of the fractured condyle. While, partial paralysis of the temporalis, the masseter and the medial pterygoid muscles helps to restore the vertical height of the mandibular ramus.

Conclusion

Botulinum toxin injection for masticatory muscle paralysis accelerates the healing process of the fractured condyle segments due to the immobilization provided. It can be applied with both closed and open reduction methods of treatment. The muscle weakening reduces the distracting forces on the fractured segments. This allows for easy manipulation of the displaced fracture during open reduction, reduces the superior overriding of the ramus, accelerates primary bone union, shortens the period of immobilization with the closed method (allows early jaw mobilization, thus, improving patient compliance), and reduces the chance of a relapse. The estimated action of the botulinum toxin lasts for about three months, which corresponds favorably with the period required for bone healing.

Despite the known benefits of botulinum toxin, its use is not very widely practiced. Factors which have possibly limited its use are: the cost of the injection and the clinical training required for its use (especially with the deeper located lateral pterygoid muscle). There is scope for future research in this field, to establish the role of botulinum toxin injection as an adjuvant therapy in condyle fracture management.

Learning points:

- Botulinum toxin injections in the muscles of mastication can be used to eliminate the excessive distracting force on the fractured mandibular condyle.
- The lateral pterygoid (inferior head) is the primary muscle involved in the anterior and medial displacement of the condyle. While the masseter, temporalis and medial pterygoid muscles pull the ramus segment up, resulting in a telescoping of the fracture, reduced ramal height, deviation of the chin, and occlusal discrepancy.
- Injection into the inferior head of the lateral pterygoid alone, or in combination with other primary muscles of mastication, can be used as an adjuvant in managing a condylar fracture. It can be used with both open and closed methods of fracture management.
- When used with the open method, the toxin injection weakens the muscle pull and helps in: easy manipulation of the displaced fracture, reduction of the superior overriding force on the ramus segment, acceleration of primary bone union, and the reduction in the chance of relapse.
- When used as an adjuvant with close reduction, it helps to reduce the required period of intermaxillary fixation. This will allow early jaw mobilization, thus, improving patient compliance.

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Chapter 6.8

Botulinum Toxin in Zygomatic Fracture Management

Kumar Nilesh, Monica Patil

Introduction

The zygomatic bone is a quadrangular shaped bone of the midface skeleton which provides prominence to the cheek. The bone also forms the vertical buttress of the midface, and supports the masticatory load during chewing. The prominent position of the zygomatic bone (also commonly referred to as the zygoma) makes it susceptible to fracture in cases of severe traumatic injuries, resulting from road traffic accidents, falls, a sports injury and interpersonal altercations.

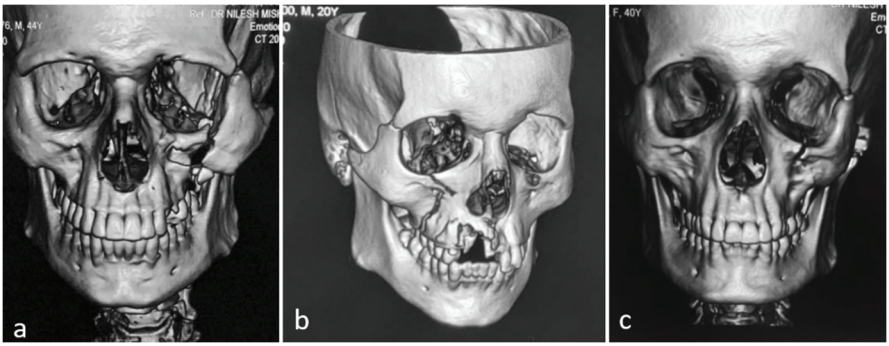

Figure 6.8A: 3D reconstruction of the computed tomography images showing; displaced zygomatic fracture (a), moderately displaced zygomatic fracture(b), and minimally displaced zygomatic fracture (c).

The management of a zygomatic bone fracture is essential both for the restoration of facial aesthetics, as well as for the establishment of masticatory function. Anatomical continuity of the zygomatic bone with its surrounding attachments, namely: the frontal, orbital and maxillary bones, to bring it back to its pre-trauma state is highly

desirable, and requires fracture fixation at multiple areas for a stable result. When the displacement of the fractured zygomatic bone is minimal, it may not require active surgical intervention (Figure 6.8A (a)). However, when the fractured segment is moderate to severely displaced, it requires surgical intervention for reduction and fixation (Figure 6.8A (b) and (c)).

Action of the muscles on a zygomatic fracture

The displacement of the fractured zygomatic bone depends on the magnitude and vector of the traumatic force. However, the role of muscular attachments in fracture displacement should also be considered. Two muscles, namely the zygomaticus major and the masseter, attach to the zygomatic bone (Figure 6.8B (a)). The zygomaticus major is a small muscle and plays a major role in facial expressions. While the masseter is a strong muscle of mastication and can provide displacing forces (in the inferior and posterior direction) on the fractured zygomatic bone (Figure6.8B (b)). Due to the force of the masseter muscle on the zygomatic bone, and the need for the stable reduction, an immobilization of the fracture segments during the healing period with multiple areas of rigid fixation is warranted for a successful outcome (Figure 6.8B (c)).

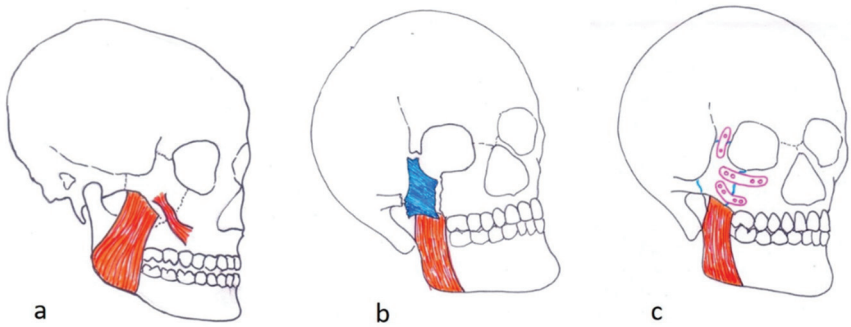

Figure 6.8B: Attachment of the masseter and the zygomaticus major muscles on the zygomatic bone (a). A downward pull of the masseter muscle on the fractured zygoma (b) and multiple areas of fixation for the stable reduction of a fractured segment.

Areas of fixation of the zygomatic fracture include: the frontozygomatic suture, the infraorbital rim, the zygomaticomaxillary buttress, and the zygomatic arch (Figure 6.8C). Depending on the

degrees of displacement, a comminution of the fractured segments and muscle forces, and a one/two/three or even four-point fixation at the zygomatic arch may be required for an undisturbed fracture healing (Figure 6.8D). Fixation may be achieved using a miniplate/microplate (commonly used), or wires (less preferred) for osteosynthesis.

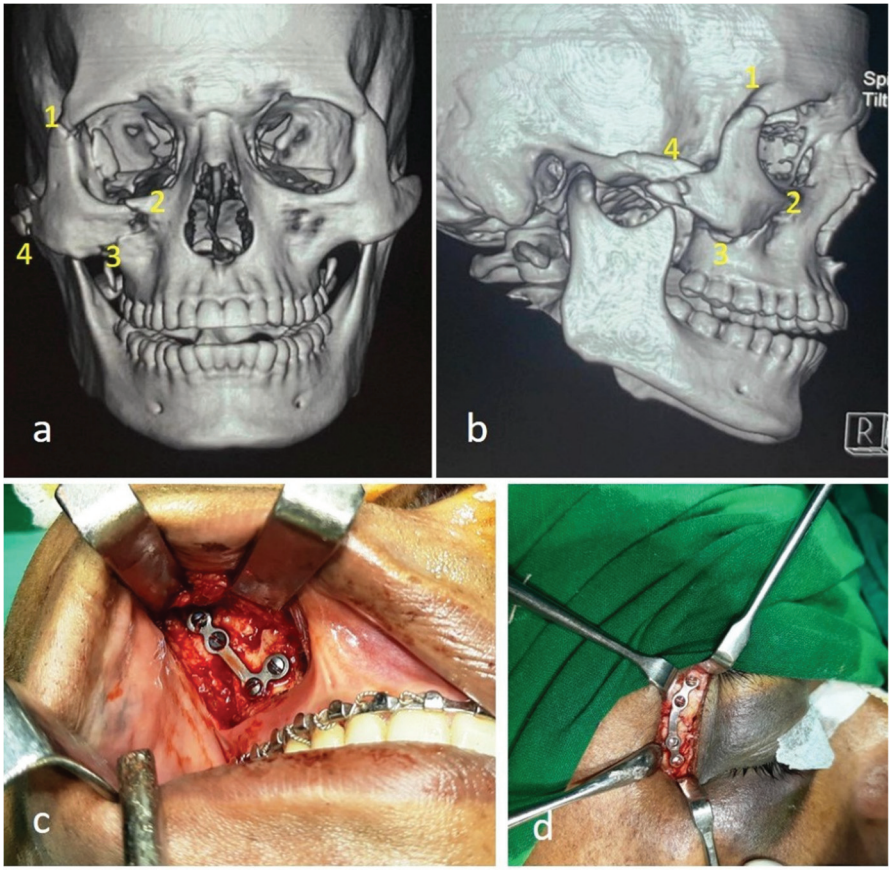

Figure 6.8C: Computer tomography images (a, b) showing a zygomatic bone fracture. Note the areas of fixation: the frontozygomatic suture (1), the infraorbital rim (2), the zygomaticomaxillary buttress (3), and the zygomatic arch (4). Clinical intraoperative images showing a 2-point fixation of the fracture at the zygomaticomaxillary buttress (c) and frontozygomatic suture (d).

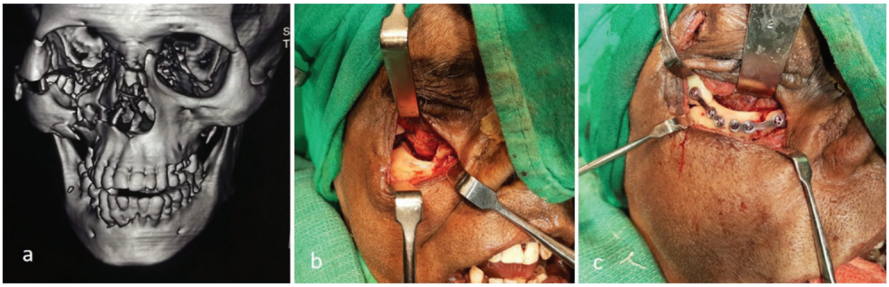

Figure 6.8D: Severely comminuted and displaced right zygomatic bone fracture (a), requiring large surgical exposure (b) and multiple miniplates for fracture fixation (c).

Use of botulinum toxin in a zygomatic fracture

With the use of botulinum toxin, a temporary paralysis of the masseter muscle at the fracture side can be achieved. This reduces the displacing force of the muscle on the fractured zygomatic bone. As the active forces from the masseter contractions are weakened, the extent and rigidity of the fixation can be reduced. The use of botulinum toxin injection into the masseter muscle can help to minimize the bone plate size used for fixation. A thin profile microplate can be used instead of a miniplate for the fixation, thus, reducing the metal volume. The thinner microplates are less palpable and adapt more easily over the contour of the facial skeleton.

The number of fixation sites can be reduced, while still maintaining a stable position of the bone during fracture healing, by using botulinum toxin injection, preoperatively, into the masseter muscle in the management of displaced zygoma fractures. Paralyzing the masseter muscle before the operative procedure reduces the displacing force at the fracture site. This allows the use of thinner plates and reduces the extent of fixation required, thus, reducing the number of incisions, the extent of the surgical exposure, and the operative time and surgical morbidity.

Although the use of botulinum toxin injection increases the overall cost of the treatment (related to the purchase and use of the toxin), the fewer bone plates required, along with less operating room utilization (reduced operating and general anesthesia time) brings down the overall cost of the fracture management.

Technique of botulinum toxin injection:

- One vial of botulinum toxin (100 IU) is diluted in 5 ml of 0.9% normal saline (to attain a concentration of 20 IU/ml of botulinum toxin-A).
- A total of 5 ml of the diluted solution is injected into the masseter muscle on the ipsilateral side (side of the fracture). A total dose of 5 ml (containing 100 IU of toxin) is injected in equally divided doses at five different points into the masseter muscle through the extraoral transcutaneous approach using a 26-gauge needle.
- A minimum depth of 1 cm should be attained during injection through the percutaneous extraoral route. A superficial injection (less than 1 cm depth of injection) should be avoided to spare the superficial muscles of the facial expression.
- The toxin achieves its peak effect within 24-48 hours of the injection. Once the toxin achieves its peak effect, the patient can be taken for the operative procedure.
- A fractured zygomatic bone is explored through the standard incisions (possibly with a lower number of surgical sites for fixation) and miniplate/microplate implants can be used for the fixation of the fractured segment to achieve a stable anatomical alignment of the zygomatic bone. In most cases of non-comminuted zygomatic fracture, a single point fixation at the zygomatic buttress is sufficient. When a displaced infraorbital rim (with or without an orbital floor fracture) is present, single point fixation at the infraorbital rim can be done, while a comminuted zygomatic fracture will require miniplate fixation at two or three sites including the infraorbital rim, the frontozygomatic suture, and the zygomaxillary buttress.

Limitations and Pitfalls

Unlike the masseter injection used for other indications (e.g., masseter hypertrophy), precaution must be taken in patients with traumatic injuries. Due to the presence of facial edema and lacerations, there can be an alteration of the soft tissue anatomy over the masseter muscle. Increased edema over the cheek and soft tissue overlying the lower jawbone requires an increased depth of penetration for the injection of botulinum toxin into the muscle mass.

Palpation of the landmarks for injection (including the borders of the mandibular ramus and the masseter muscle) before the injection technique can be difficult due to the swelling and pain associated with a trauma. A greater degree of clinical training and experience with botulinum injections is required in such situations for a favorable outcome and to avoid complications, such as a superficial injection into the muscle of the facial expression.

Despite the potential benefits of botulinum toxin injection in the management of a zygomatic fracture, its use in clinical practice has been limited. There is a lack of consensus in the literature regarding the role of the masseter muscle on a displacement of the fractured zygomatic bone. Some authors believe that it is more often the improper positioning of the bone after reduction that weakens the stability of the fracture segments, rather than the pull of the masseter muscle. Santo et al. in their study on ten zygomatic fractures, showed that the masticatory force of the masseter (measured by bite-force, electromyographic study, and a radiographic assessment of the muscle vectors) was considerably reduced after trauma.[1] Panchanathan et al. made a similar observation in 20 patients with a zygomatic fracture who were evaluated for the function of the masticatory muscle by bite-force measurement, electromyography of the masseter and temporalis muscles and measurement of the mandibular movements. Although there was a significantly reduced function of the masseter muscle after trauma, a gradual recovery in its function was seen postoperatively throughout the follow-up period of six months.[2] Although the results of the above-mentioned studies show that masseter muscle function is reduced after trauma, the existing force may still be higher than the threshold level required for a displacement of the fractured zygoma. A fracture of the zygoma, with complete disjunction from the surrounding bones (a tripod fracture) and a comminuted fracture, further reduces the muscle force required for displacement, thus, necessitating the use of multiple rigid fixations. Kayikçioglu et al. published a successful outcome of the use of botulinum toxin on the masseter muscle before the management of tripod and comminuted zygomatic-complex fractures.[3] The fixation site was reduced to a single one in most of the cases. While no postoperative complication or change in facial topography due to muscle atrophy was noted, the masseter muscle regained its normal function after three to six months.

Learning points:
➢ The masseter muscle can be a cause of the post reduction displacement of the fractured zygomatic bone; it is capable of exerting forces that are sufficient to displace the bone inferiorly when inadequately fixed.
➢ Muscle paralysis may guarantee fixation of the fractured segment as well as enable the use of fewer fixation sites and the use of weaker plate systems.
➢ This helps to reduce the use of mini or microplates and, thus, reduces the number of surgical sites, consequently, reducing the scar and operative time.
➢ By reducing the tension on the fractured segments, the use of microplates can be opted for over miniplates.
➢ Injection into the masseter muscle is made by injecting 100 IU of the toxin in five divided doses across the masseter muscle of the involved site. The depth of injection should be kept at 1 cm to avoid a superficial injection into the muscle of the facial expression.

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Chapter 6.9

Role of Botulinum Toxin in Dental Implantology

Aaditee Vande, Monica Patil, Kumar Nilesh

Introduction

Dental implants have become one of the most efficient treatment modalities in the replacement of a missing tooth, or teeth. The basic concept of dental implantology involves the integration of the implant with the jawbone, which is termed "*osseointegration*". Traditionally, once the dental implant is surgically placed into the bone, a period of undisturbed healing (varying from three to nine months) is allowed for the union of the implant surface with the surrounding bone, before it can be functionally loaded (with a prosthetic tooth). However, the ever-increasing functional and aesthetic demands of patients have encouraged implantologists to reduce the treatment period by loading the implant immediately at the time of placement, or after a reduced period for osseointegration.

The immediate loading of the dental implant clearly represents a change in the conventional principles of implantology. Therefore, a stress-free healing period has to be considered as an absolute prerequisite to achieve the goal of osseointegration. One of the factors suggested for succeeding with immediate implant loading is controlling the functional forces on the implant body. Both the prophylactic and therapeutic use of botulinum toxin can play a significant role in the future of dental implant therapy.

Prophylactic role of botulinum toxin

Implants are often considered for the replacement of a missing tooth or teeth in the areas of higher masticatory load. When the tensile stress in the bone around the area of the implant placement is higher, it may often result in bone resorption, thus, creating unfavorable conditions for the osseointegration of the dental implant. The prophylactic use of

botulinum toxin holds promise in reducing the masticatory load in such conditions if used just before and during implant therapy.

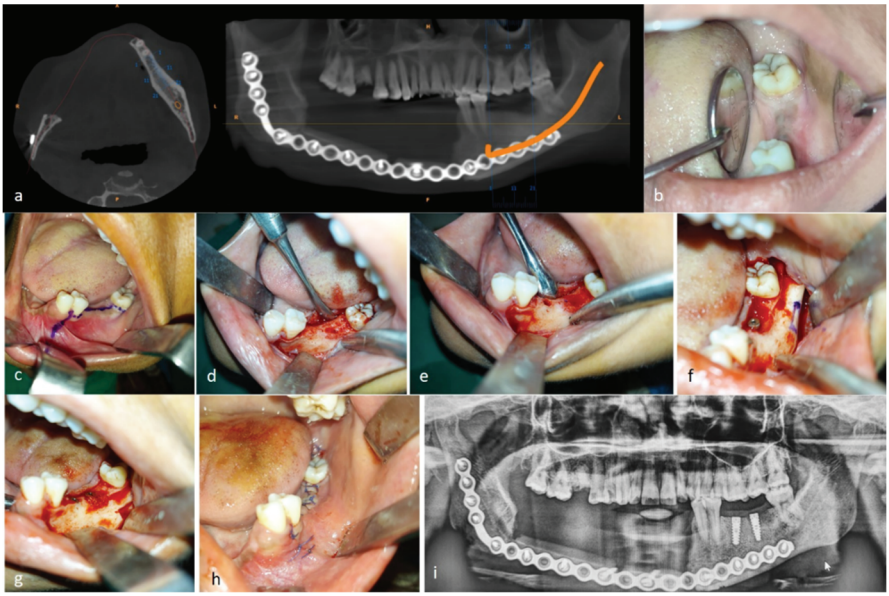

Figure 6.9A: Images showing placement of dental implants in the lower jaw previously operated for surgical removal of jawbone tumor by hemi-mandibulectomy, requiring placement of dental implants on the contralateral side. Cross-sectional cone beam tomography image and panoramic view showing the defect on the right side of the mandible and edentulous area for implantation on left side (a). Surgical steps in implant placement: edentulous region (b), incision marking (c), exposure (d), osteotomy for implant placement (e), implant placed, with area of implant thread exposure with implant at 37 region and autogenous graft harvest site on external oblique ridge (f), and closure (g). Post-operative panoramic radiograph showing placement of implants in left hemi-mandible. Lack of balanced occlusion, unilateral masticatory forces, and a reduced number of teeth, increases the overall loading on the implant. Use of a prophylactic botulinum toxin injection in the masseter muscle can reduce the loading forces in the initial period of bone-implant integration after immediate loading in such cases.

Traditionally, a reduction of the masticatory load has been achieved using: interceptors, splint devices or transcutaneous electrical nerve stimulation (TENS) therapy.[1] Although the above modalities can decrease the load on the bone-implant interface, they are of limited use. Though interceptors and prefabricated occlusal splints result in an alteration of the location and the pattern of increased masticatory forces, the limited reduction does not significantly improve the outcome. TENS therapy is also seen to provide masticatory muscle relaxation only for a limited time period. The above strategies do not provide sufficient protection against deleterious involuntary nocturnal mandibular excursions or nocturnal changes in the mandibular position.

The prophylactic administration of botulinum toxin appears to be a sensible adjunct in implant therapy, especially in the areas of high masticatory load, abnormal bone tensile force and when immediate loading or a reduced osseointegration time is desired (Figure 6.9A). Injecting botulinum toxin prior to, or during, the time of implantation of immediately loaded implants has been reported to control the functional forces, thereby, improving the implant survival and functional outcome.[1, 2]

The Therapeutic role of botulinum toxin

The main determinants of dental implant failure are: low bone volume, poor bone quality and excessive masticatory loading. Osseointegration of an implant is a dynamic process and is critical for the establishment and maintenance of a functional implant. Even after successful initial osseointegration, an implant can fail. This failure can be due, either to a local infection or failure at the bone-implant-restoration interface due to excessive or inappropriate loading. High muscular forces, increased occlusal load and unexpected temporomandibular joint position can be the contributory causes in such situations, resulting in implant failure. To avoid this, a reduction in the masticatory forces is necessary. Botulinum toxin can be of therapeutic use for the purpose of preserving the bone-implant-restoration system in patients with an unstable or failing implant, due to excessive muscle force and loading, once a local cause of infection has been ruled out.

Role of botulinum toxin in basal implant therapy

Another potential area of use orf botulinum toxin, both prophylactically and therapeutically, are for basal implants, also popularly referred as

bi-cortical implants. This implant system has gained popularity over the past decade with the benefit of providing immediate replacement of missing teeth in regions with severe bone deficiencies. The above-mentioned benefits of use in an atrophic jaw, along with immediate loading, also increases the potential risk of failure.

Treating cases of severe bone atrophy with basal implants requires the use of long prosthetic cantilevers for the correct restoration of the vertical dimension, which increases the risk of overload. By the immediate loading of restoration, the newly created occlusal surface is included in the masticatory process. The choice of a basal implant, especially in the case of severe alveolar bone atrophy, also means that after the prosthetic restoration and loading there is a sudden increase of the vertical dimension, which, consequently, may change the parameters of the masticatory function unfavorably. The use of basal implant therapy can alter the pattern of the masticatory muscle function, the position of the jawbone, and the relative position of the dental arches. The voluntary control of the patient, to large extent, allows a congruent and synchronized use of both the arches in the daytime. However, when the control is absent (during sleep) the jaws tend to approximate in positions that greatly deviate from their normal daytime positions.[1]

Both the therapeutic and prophylactic administration of botulinum toxin, especially in the early phases of the basal implant therapy, can be potentially beneficial, when such unfavorable masticatory forces may mobilize the implants. The toxin therapy can reduce the risk of damage to the bone-implant interface caused by immediate loading, increased masticatory force, altered inter-arch alignment, changed mandibular position, and involuntary excessive nocturnal loading.

Method of use:

The technique of use of botulinum toxin as a therapeutic or prophylactic adjunct in dental implantology is not clearly outlined in the literature. This is definitely an area of future research, as most of the data presently available is sparse and the guidelines are purely anecdotal. The protocol and parameters that are yet to be established include: definite indications, dosage, the sites of the injection(s), and the muscle(s) to be treated.

Indication:

The indications for use of the toxin are: an immediately loaded implant, an implant in the area of high masticatory force, failing implants (for reasons not related to infection), and extensive basal implant therapy. However, a correction of the detrimental risk factors such as unilateral loading and premature contact should be managed before the toxin therapy.

Dosage, site of injections/muscle(s) treated:

The injection can be made unilaterally or bilaterally based on the side, site, number of implants, muscle load and hypertrophy. However, a bilateral injection of botulinum toxin into the masseter muscles (without treating the temporalis muscle) is usually sufficient to achieve satisfactory results. Injections into the temporalis muscle are rare and are indicated in cases of severe atrophy, or significantly high masticatory loading.

The recommendation of dosage is based on previous experience of use of the toxin for other maxillofacial conditions.[3] It is usually advisable to inject into both the masseter muscles. The administration of a full dose of 200-250 IU of botulinum toxin into each masseter muscle can result in an adequate reduction of the chewing forces for up to eight weeks. Although a long term reduction of the masticatory load is never the objective of the therapy, the initial period of weak muscle action gives time for achieving sufficient osseointegration at the bone-implant interface. A low dose is indicated when the bone volume and quality is better and also in conditions where the primary implant stability is adequately achieved during implant placement. The dose can be titrated as per the need and repeat injection(s) can be given if the desirable level of action is not attained.

Conclusion

The risk of failure of the dental implant therapy is higher in patients with low bone volume and quality, as well as in patients with unfavorable and high masticatory forces. The increased desire for immediate restoration of missing teeth, for functional and aesthetic purposes, presents special challenges to the implantologist in such situations. An immediate loading of the implant or a short duration of osseointegration can have a detrimental effect on the treatment

prognosis in such situations.

The prophylactic administration of botulinum toxin may facilitate a reduction of the strength of the masseter and temporalis muscles after implant placement, especially in the case of immediate loading. Bone-implant-restoration systems can become mobile due to a functional overload on the peri-implant bone during function. The therapeutic use of botulinum toxin in such cases, if instituted early, can reduce the masticatory load on the bone-implant junction, reversing bone loss and promoting osseointegration. However, further studies need to be carried out to establish, scientifically, the use of botulinum toxin in dental implantology, especially with respect to the recommended dosages, the muscles to be treated, and its long-term affect.

Learning points:
➢ With the success of dental implant therapy, more patients and implant surgeons desire the immediate restoration of aesthetics and function by immediately loading the dental implant, thus compromising on the conventional period given for osseointegration.
➢ One of the most critical factors for the success of an immediately loaded implant is controlling the functional and masticatory forces to prevent implant failure.
➢ The prophylactic use of botulinum toxin can play a significant role in immediate loading of dental implant therapy, by reducing excessive masticatory load.
➢ The therapeutic administration of botulinum toxin can preserve a failing bone-implant-restoration system, when the cause is not related to infection.
➢ The bilateral injection of botulinum toxin into the masseter muscles, with or without treating the temporalis muscles, is generally advocated to achieve a satisfactory reduction of the masticatory load.
➢ Future studies to establish the guidelines for the indication, dosages, and muscles to be treated, are required for long term use of the toxin in this field.

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Chapter 6.10

Botulinum Toxin in the Management of Bruxism

Aaditee Vande, Monica Patil, Kumar Nilesh

Introduction

Bruxism is a parafunctional activity that includes tooth clenching, bracing, gnashing and/or grinding. It is defined as a "repetitive jaw-muscle activity which is characterized by clenching or grinding of the teeth, with or without bracing or thrusting of the mandible". Bruxism manifests in two clinical forms: sleep bruxism (occurs during sleep) and awake bruxism (occurs during wakefulness). The prevalence of bruxism varies widely, ranging from 5 to 96 percent in the adult population. Bruxism is of great interest to dentists, oral surgeons, psychologists, neurologists and primary care physicians. The clinical manifestations of the disorder are enumerated in Table 6.10A. The nocturnal bruxism criteria, according to the International Classification of Sleep Disorders, are presented in Table 6.10B.

Many etiologic factors, such as emotional stress, occlusal interferences, neurological disorders, and certain drugs, have been implicated in bruxism. However, the exact pathophysiology is still unknown. Bruxism seems to have a multifactorial etiopathogenesis mediated by the central and autonomous nervous systems. Certain neurological disorders, such as Rett syndrome, mental retardation, anoxic encephalopathy, and cerebellar hemorrhage are associated with bruxism. These neurological disorders manifest as abnormal spasms and movements involving the oro-lingual-facial musculature. Patients with idiopathic and post-traumatic cranial dystonia have reported tooth clenching and grinding.[1, 2] A majority of these patients present with diurnal symptoms, though some present with both diurnal and nocturnal symptoms. While no central nervous system structures associated with teeth grinding have been identified, it has been speculated that, in some cases, bruxism may be a part of

dystonia and share a similar pathophysiology. In cranial-cervical dystonia, a higher prevalence rate of bruxism has been reported.[3]

Table 6.10A: Clinical features of bruxism
▪ Tooth abrasions
▪ Dental mobility
▪ Fracture of dental restorations/fillings
▪ Masseter muscle hypertrophy
▪ Pain in the muscle of mastication (myalgia)
▪ Pain in the temporomandibular joint (arthralgia)
▪ Symptoms of temporomandibular joint disorder (joint pain, clicking, reduced mouth opening, joint stiffness, deviation of the jaw)

Table 6.10B: Nocturnal Bruxism Criteria according to The International Classification of Sleep Disorders (ICSD 2nd Edition)
A. The patient reports, or is aware of, tooth-grinding sounds or tooth clenching during sleep.
B. One or more of the following is present: ▪ Abnormal wear of the teeth ▪ Jaw muscle discomfort, fatigue/pain and jaw lock upon awakening ▪ Masseter muscle hypertrophy upon voluntary forceful clenching
C. The jaw muscle activity is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder

Various treatment modalities have reportedly been used in bruxism. However, there is no general agreement as to what is the best

therapeutic option. Conventional treatment options using occlusal splints, drugs (benzodiazepine, L-dopa), and cognitive-behavioral therapy, have limited efficiency. The above available options do not seem to solve the underlying cause, and only treat the signs and symptoms associated with bruxism and prevent the destructive effect of muscle hyperactivity and teeth grinding on the associated anatomical structures.

Botulinum toxin is one of the most potent biological toxins. It is safe and effective for the treatment of various forms of neurological disorders. The application of botulinum toxin is suggested to reduce the number of bruxism events. The beneficial effect of the toxin is due to the reduction of peripheral muscle activity, possibly without any action on the central nervous system. A single dose of botulinum toxin injection into the masseter muscle may totally inhibit severe bruxing behavior.

However, it is hypothesized that masticatory muscle paralysis by the botulinum toxin can also disrupt the feedback loop from the trigeminal motor nucleus and, thus, inhibit the central bruxism generator. It is also believed that the toxin possibly deactivates the periodontal mechano-receptors during mastication, which is thought to have a facilitatory effect on the motor neurons involved in jaw closure. There has also been a reported case of the total resolution of bruxism caused by a brain injury after a single injection of botulinum toxin.[4]

Technique of use of botulinum toxin in bruxism:

The patient is examined and information is collected regarding:

- Demographic details
- Etiology of bruxism
- Duration of bruxism
- Associated dystonia or movement disorders in other body parts
- Family history of bruxism or movement disorders
- Site and number of botulinum toxin injections required
- Mean and cumulative muscle dose to be administered
- Number of treatment visits required.

Technique:

- After diagnosis, the patient is prepared for botulinum toxin injection.
- Botulinum toxin is injected into the masseter muscle at three sites.
- The subject is asked to clench and the first site selected is the most prominent part of the masseter muscle observed.
- The other two sites are 5 mm inferior from the first point, anteriorly and posteriorly.
- The dose of botulinum toxin ranges between 25 and 40 IU. However, up to 50 IU can be used in divided doses at three points of injection in severe cases. Additional injections into the temporalis muscle can also be given.

Conclusion

Bruxism is a disorder which results in a condition leading to facial pain, headache, arthralgia, wearing of the teeth, and muscle hypertrophy. Conventional management has a limited effect in treating the pain and masseter hypertrophy associated with teeth grinding and clenching. Botulinum toxin injections into the masseter (and temporalis muscle when required) reduces the frequency of bruxism episodes. It decreases the degree of pain and the total masticatory force, thus, offering desirable clinical results. Use of botulinum toxin injections reduces the intensity of bruxism and can be more frequently used as a novel therapeutic option for management of bruxism in the future.

Learning points:
▪ Bruxism is a nocturnal or diurnal parafunctional activity that includes teeth clenching, bracing, gnashing and grinding.
▪ The application of botulinum toxin injection into the masseter muscle is suggested to reduce the number of bruxism events, by diminishing the peripheral muscle activity.
▪ The dose of botulinum toxin ranges between 25 and 40 IU. However, up to 50 IU can be used in divided doses at three points of injection of the masseter muscle.

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Chapter 6.11

Botulinum Toxin in the Management of Trismus

Monica Patil, Kumar Nilesh

Introduction

In broad terms, *trismus* means reduced mouth opening and results from a wide variety of conditions. The local cause of trismus can be broadly divided as intra-articular and extra-articular. The intra-articular causes are localized within the joint space and include: ankylosis, arthritis, synovitis and disc pathology, whereas the extra-articular causes (usually present around the temporomandibular joint area) include: trauma, pathology and infections. Systemic causes are uncommon and include infections such as tetanus, meningitis and a brain abscess. Certain drugs and psychological disorders such as hysteria are other rare systemic causes of trismus. Trismus is also seen in certain neurological conditions with severe generalized spastic movement disorders. It arises as a clinical complication caused by stroke, traumatic brain injury, and hypoxic encephalopathy and results in muscular hypertonia of the jaw muscles.[1]

Jaw movements are severely disturbed because of spastic trismus. It results in severe functional disturbances affecting swallowing, speaking, mouth opening, mastication and oral hygiene maintenance. It is also associated with muscle pain and leads to bruxism, which is detrimental to the teeth (causing wearing, attrition and dental fractures).

A standard therapeutic protocol to control the muscular hypertonia in spastic trismus is not available. Functional therapies offer limited remedy and do not have a sustained and permanent effect. Oral pharmacological regimens have been traditionally used to reduce the muscle tone. However, they are often associated with reduced levels of consciousness, and diminishing alertness and attention.

The efficacy of botulinum toxin to treat dystonic muscular hyperactivity in cervical dystonia as well as in spastic overactive muscles has been demonstrated successfully by various studies. Botulinum toxin therapy was recently introduced as a new approach for treating trismus, as it is known to reduce the muscle tone. When locally injected, it reduces the cholinergic peripheral neurotransmission for a limited period of time. Local injections with botulinum toxin into the jaw muscles reduce hypertonia, which can be used as a rationale for the symptomatic therapy of trismus.[2]

Technique of botulinum toxin injection:

- The distance between the upper and the lower incisor teeth (inter-incisal distance) should be measured. It can be done by carefully inserting a wooden spatula between the incisor teeth and using a scale or vernier caliper. Recording hist before injecting the muscles with botulinum toxin is important to provide documentation of the pre-operative mouth opening and to monitor the treatment progress.
- Patients should be injected at their first visit with botulinum toxin into each masseter muscle. Both muscles should be injected at two or three injection sites each. Electromyographic guidance can preferably be used when available and desired (Figure 6.11A).
- Patients should be examined weekly after their first injection to study its effects.
- At the third visit, depending on the clinical course, the treating physician can decide whether or not to perform a second injection.
- The patient can be treated again with botulinum toxin injection into each masseter muscle when a greater degree of muscle paralysis is desired. As a modification of the first injection, the temporal muscles can also be injected during this second session.
- At the ninth week after the first injection the patient is re-evaluated. The distance between the upper and the lower incisor teeth should be recorded to assess the improvement in condition.

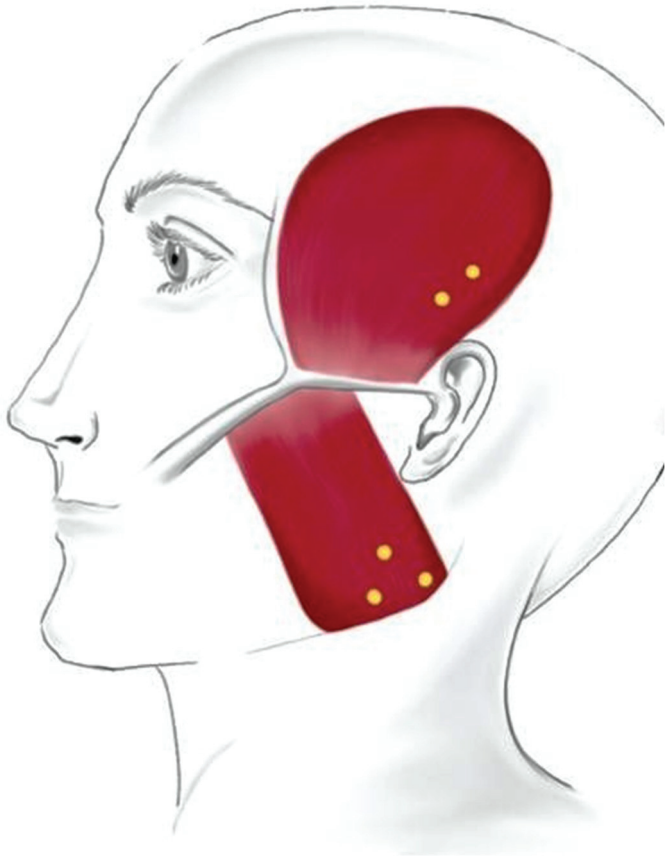

Figure 6.11A: Injection sites of the botulinum toxin (three sites per masseter and two per temporalis muscle).

Complications:

There is always a possibility that the intramuscularly injected botulinum toxin may diffuse, affecting the neighboring structures that are also cholinergically innervated. Although this is not desired, it is difficult to avoid. A local spread of the toxin is inevitable even if small volumes and low doses are injected at the sites. When the injection is targeted into the masseter muscles, botulinum toxin may diffuse

locally into the parotid gland and affect salivation.[2, 3] The facial nerve present within the substance of the parotid gland may also be involved, leading to reversible facial palsy. However, these complications are usually rare, reversible and are mild to moderate in intensity.

Conclusion

Spastic trismus can be successfully treated with botulinum toxin. Botulinum toxin reduces the muscle tone in the masseter muscles and improves mouth opening. The treatment goals that could be achieved through this therapy include: improved hygiene of the mouth, reduced bruxism, and improved mouth opening allowing for better feeding.

Learning points:
▪ Trismus is muscular hypertonia of the jaw muscles caused by a variety of disorders.
▪ Patients should be injected in each masseter muscle at two to three injection sites each.
▪ As a modification of the first injection, the temporal muscles can also be injected in this second session if a greater effect is desired for improvement in outcome.

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Chapter 6.12

Application of Botulinum Toxin in Myofascial Pain Dysfunction Syndrome

Monica Patil, Kumar Nilesh

Introduction

Myofascial pain dysfunction syndrome (MPDS) is a regional pain disorder of muscular origin characterized by the existence of trigger points within the muscles. According to the description by Schwartz, it is characterized by temporomandibular joint clicking and pain, muscle tenderness and restricted mouth opening.[1] Presently, (MPDS) is defined as a "Regional myogenous pain condition which is characterised by local areas of firm hypersensitive bands of muscle tissue, known as trigger points".[2] The myofascial trigger point is in turn, defined as a palpable and hyperirritable nodule located in a taut band of muscle. Stimulation of any of these points produces two characteristic phenomena: sudden contractions of the taut band, called local twitch response, and referred pain.[3]

The conventional treatment of MPDS includes: pharmacological agents, splint therapy, or both. However, they are known to produce only temporary relief of the painful symptoms. Long term use of pharmacological treatments can be associated with side effects such as gastrointestinal disorders, drug interactions, and adverse reactions. Thus, their use for long periods of time is not recommended.

Etiopathogenesis and clinical features

Although the pathogenesis of MPDS remains difficult to understand, there are a number of mechanisms that have been attributed to it:

- Continuous source of input leading to deep pain
- Heightened emotional stress
- Sleep disturbances

- Local factors that govern muscle health (habits, posture and muscle strain)
- Systemic factors (nutritional deficiencies, poor physical status, chronic fatigue and viral infections).

These causes result in the parafunction of the masticatory muscles, in turn, resulting in its spasm leading to MPDS.

Clinically, in MPDS, the patient displays a decreased range of mandibular movement, which usually correlates to the location and intensity of the pain. The patient usually describes the pain as a dull ache or pressure. However, rarely, it can be throbbing and severe. The masticatory muscles are tender on palpation. There are identifiable areas of tenderness (trigger points) on palpation of the affected muscle. These trigger points are described as firm knots within the involved muscle(s). These areas are typically more tender on palpation than the surrounding muscle tissue. The pain which is usually experienced within the muscle may occasionally elicit referred pain to a distant site(s). Any of the primary muscles of mastication may be involved in MPDS, along with the accessory cervical or pericranial muscles. However, the muscles involved in the closing of the jaw i.e., the masseter, the medial pterygoid and the temporalis are most commonly affected. The clinical features of the disorder are summarized in Table 6.12A. Clinically, the diagnosis of MPDS is confirmed by temporary inactivation through anaesthetic injection made at the trigger points using local anaesthesia, vapo-coolant sprays or transcutaneous electrical nerve stimulation.[4] If the involved muscle is tender on palpation and none of the other masticatory muscle disorders better describe the patient's condition, the suggested diagnosis is MPDS.

Table 6.12A: Clinical features of MPDS
▪ Pain in the temporomandibular joint region
▪ Clicking/popping noise on mouth opening
▪ Restricted mouth opening
▪ Deviation of the mandibular midline to the affected side on mouth opening before clicking
▪ Restricted laterotrusive jaw movements

The role of botulinum toxin in MPDS

It is hypothesized that the pathogeny of MPDS is related to the increased activity of acetylcholine (ACh) at the neuromuscular junction of the involved muscle(s).

Increased ACh activity results in a sustained contraction of the striated muscle tissues, which explains the development of the taut bands in MPDS.

A prolonged and sustained muscle contraction leads to a greater local energy demand and an energy crisis.[5] The release of chemical mediators from the hyperactive muscle fibers and the extracellular fluid around the trigger points cause local muscle pain.[6] The phenomena is similar to that seen in muscle ischemia and during strenuous exercise. The metabolic condition further sensitizes amines, which, in turn, stimulate the nociceptors, giving rise to myalgia and pain characteristic of MPDS.[7] To summarize, there are two events that explain the myofascial trigger point is MPDS:

- Altered acetylcholine activity at the neuromuscular junction, and
- Nociceptive stimulation.

In recent decades, botulinum toxin has been increasingly used for the treatment of numerous disorders characterized by muscle hyperactivity. Botulinum toxin blocks the neurotransmission at the neuromuscular junction. Various transport proteins are involved in the process of release of ACh at the neuromuscular junction. These proteins aggregate to form the SNARE complex that are responsible for the fusion of the ACh-containing vesicles with the aggregate protein receptors on the cell membrane at the neuromuscular junction. As the ACh vesicles fuse with the cell membrane, it subsequently releases the neurotransmitter at the nerve-muscle junction. The heavy chain of the botulinum toxin has a higher affinity for the membrane receptors. After binding with the receptors, the botulinum toxin molecule undergoes endocytosis.[8] The light chain of the toxin is released within the cell, where it acts as a zinc-dependent endoprotease.[9] Botulinum toxin causes a cleavage of the SNARE complex proteins. As the formation of the complex is inhibited, ACh is not released at the neuromuscular junction, thus preventing muscle hyperactivity. This property of the botulinum toxin molecule

can be explored for the blockade of increased activity of acetylcholine which precipitates the symptoms in MPDS.

Technique of botulinum toxin injection:

- A vial of botulinum toxin (containing 100 IU) is diluted in 2 ml of normal saline. The reconstituted mixture contains 5 IU of botulinum toxin per 0.1 ml of the solution.
- An insulin syringe is used for the injection and 0.5 ml of solution containing 25 IU is drawn for usage.
- The injections are made at the trigger points (which are usually localized at the masseter and temporalis muscles). To localize the site of the injections at the trigger points, the muscle is palpated along its entire area. Once the trigger point is touched, the patient usually has a painful reflex. This confirms that the injection has been made into the trigger points.
- The masseter muscle is approached transcutaneously with the needle directed towards the trigger points. Aspiration before injecting is mandatory to avoid an inadvertent intravascular injection. The solution is injected slowly, over a period of 5-10 seconds, at the trigger points.
- Similarly, the temporalis muscle is examined for the available trigger points. The needle is inserted through the skin at the localized sites and the solution is deposited.
- The total volume of solution deposited can vary, based on the severity of the symptoms and the number of localized trigger sites. However, the guidelines for injection in the masseter and temporalis muscle are broadly presented in Table 6.12B.

Table 6.12B: Units for injection into the involved muscles

Masseter muscle	Temporalis muscle
25 IU	15 IU

Limitations of the use of Botulinum toxin for MPDS

- The botulinum toxin action is only able to relieve the symptoms and does not address the underlying cause.
- Therapy with botulinum toxin is temporary. The treated muscle function returns back to its original activity within one to three months and, thus, retreatment is invariably required.[10]

Learning points:
▪ Botulinum toxin is a novel treatment option for myofascial pains. It is safe, reversible and has a high potency.
▪ The disorder underlying MPDS is correlated to inappropriate activity at the neuromuscular junction. Botulinum toxin blocks neurotransmission, bringing about relief from the symptoms of MPDS.
▪ The masseter and temporalis muscles appear to be responsible for MPDS and, hence, are the most commonly targeted muscles in botulinum toxin therapy.
▪ Injections are made using the compression of the trigger point technique. It helps to confirm the needle position within the trigger point of each target muscle.
▪ A total volume of about 25 IU and 15 IU is deposited into the masseter and temporalis muscles, respectively.
▪ Botulinum toxin therapy is a temporary treatment modality and the muscle function returns back to its normal activity within a few months, requiring retreatment.

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Chapter 7

The Future of Botulinum Toxin

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In the past 30 years, the world of botulinum toxin has changed significantly. Applications of the drug have come a long way since 1982, when Oculinum was the only available product for clinical use. The concept of using the most deadly poison to treat muscle disorders was rapidly reported in various popular publications following the initial report in the Reader's Digest and the National Enquirer. At that time, the indication for the use of botulinum toxin was limited to the treatment of strabismus. Blepharospasm and hemifacial spasms were soon added to the list. After the FDA's approval in 1989, several other indications followed.

The field of botulinum toxin is expanding so rapidly, that it wouldn't be wrong to say that researchers are lagging behind in scientifically investigating the efficacy and safety of the newer indications. Botulinum toxin has been used to treat glabellar lines for more than 15 years before the regulatory studies began and more than 20 years until the FDA's approval. This somewhat limits the clinical uses of the toxin and, hence, various applications may be speculative and opinionated.

Newer indications

With the increased understanding of the mechanism of action of the botulinum toxin, there have been great extensions in its use. For example, the use of botulinum toxin for cosmetic purposes led to its recognition as a treatment option for headaches and migraines, as some individuals experienced an improvement.

A wide range of conditions that involve abnormal muscle function, excessive glandular function, and pain are now being treated with botulinum toxin. Conditions that are recognized as being worsened by excessive sweating such as benign familial pemphigus, can be

improved by botulinum toxin injections in those areas. Use of the toxin in specialized areas of oral and maxillofacial surgery, such as traumatology, implantology, the temporomandibular joint and salivary gland disorders is yet to be extensively explored and provides an avenue for future study and clinical application.[1-5]

Topical formulations

Up to the recent past, it was presumed that because of the large molecule size of botulinum toxin, it would be difficult for it to pass through intact skin, thus, precluding the possibility of a topical formulation. The effectiveness of a topical formulation was believed to be doubtful. However, recently published pilot studies show promising results and prove these assumptions incorrect.[6, 7]

The advent of nanotechnology has allowed the delivery of large molecules into the skin, which, otherwise, cannot penetrate the corneal layer of the skin. In the initial clinical trials two companies, namely Transdermal Corp. Michigan, and Revance Therapeutics, California, have published reports on the topical delivery of botulinum toxin for management of facial wrinkles and hyperhidrosis. The use of nanotechnology provides a noninvasive transdermal drug delivery technique while preserving the bioactivity of the botulinum toxin, without denaturing them. The active ingredients in the cream allow the botulinum toxin to be stable at room temperature for prolonged periods, ensuring its safety and efficacy. It is believed that there is a delivery of the toxin molecules deep enough into the skin, which provides the same effect as he injectable form. With the use of nanospheres, the toxin is delivered into the skin without any skin damage or systemic toxicity.[8] This offers an avenue of use of needle-free, pain -ree application in the future, especially for the management of facial wrinkles and the treatment of excessive sweating (axillary and palmo-plantar hyperhidrosis).

The ability to be able to topically apply botulinum toxin on the face will solve many queries and its effect on the sebaceous glands, flushing, telangiectasias, etc. will be uncovered. So far, various experiments have been done with different concentrations in order to produce the desired effects of the toxin. Its availability to clinicians in the immediate future is expected to be selective and the durations for application of the gel in different regions for different indications will be the topic of interest. It will definitely be an exciting new era in the field of botulinum toxin when topical products are more commonly

available for clinical use.

However, a word of caution for the topical formulation should be noted at this stage, especially in the hands of the common man and the inexperienced or undertrained patient. Its availability for general use and in the general public could lead to misuse of the product. There is the possibility of: its application in non-indicated areas, improper application, overuse, use in patients in whom it was not initially prescribed or in whom it is contraindicated. Table 7A summarizes the potential benefits and limitations of the topical formulation.

Table 7A: Potential benefits and limitations of a topical formulation of the botulinum toxin

Benefits	Demerits
▪ More patient compliance ▪ Pain-free (without injection) ▪ Ease of application in areas where injection is difficult e.g., the lip, neck ▪ The formulation preserves the bioactivity of the toxin and is stable at room temperature for prolonged periods ▪ Depth of penetration comparable to injection	▪ Potential for overuse ▪ Use in non-indicated areas ▪ Use for non-indicated cause ▪ Lack of expert monitoring of dosage and area of application

Mesobotox

There have been many discussions on Mesobotox in cosmetic treatments and whether or not it is effective. Mesobotox is a cosmetic procedure that can reduce fine lines and wrinkles, resulting in smoother, younger-looking skin. The technique of Mesobotox is known to reduce pore size and oil production. It also decreases facial sweating. Unlike the traditional botulinum toxin treatment, where the solution is injected into the muscle layer, in Mesobotox the toxin is

injected into the deeper level of the skin resulting in:

- Immediate facial smoothness
- Smaller pores
- Reduced sweating.

This procedure is similar to botulinum toxin injections. However, Mesobotox uses a microneedle and a small amount of diluted toxin. The solution is injected in a widely distributed area throughout the skin.

Toxin molecule modifications

For a long time, scientists and clinicians have tried to modify the toxin structure, changing its duration of action and target molecules.

Duration of effect:

A short duration toxin can be used in conditions such as healing of a post-traumatic wound or during the post-operative period, when it might be necessary to rest an area for a short period of time (e.g., immobilization of the underlying muscle bed for a period of one to two weeks after suturing of a facial laceration). A reduced duration of action would reduce the inconvenience for an individual to tolerate the paralytic effects of the toxin for three months or more. A modification of the toxin molecule to achieve this can be a potential area for research in the future.

The next, and totally opposite, desired property of the toxin will be to increase the duration of its effect. This is probably the most desired modification expected when a prolonged action of the toxin is required (for example in the management of facial wrinkles). It would indeed be a delight to patients if the effect could be increased by 50% or more, thus, reducing the number of sittings, thus, bringing down the treatment cost. Some evidence suggests that this might be possible in the future.

Target of action:

This is a speculative part of the research. The botulinum neurotoxin consists of three parts:

- The binding domain
- The translocation domain

- The endoprotease.

Changing one of these domains to achieve a change in the target or duration would produce interesting results. For example, adding the toxins endopeptidase to a different heavy chain would change the target of the enzyme but not the action. There are ongoing experiments that have created engineered forms of botulinum toxin using the endopeptidase portion of the toxin in fusion with various targeting moieties that allows the selective targeting of a specific cell type. If successful, this will lead to dramatic changes in the clinical use of the toxin.

Botulinum toxin is, without a doubt, an amazing molecule. Every time the world has understood its actions and its varied clinical applications, we have been illuminated by yet another action and interaction. Botulinum toxin will widen the horizons of its use even more in the future.

Learning points:
➢ The future of clinical application of botulinum toxin is ever expanding and involves various disciplines across medicine, surgery and dentistry.
➢ The possibility of the use of a topical formulation of the toxin is currently being explored. The use of nanotechnology driven local drug delivery holds the potential for local, painless, self-administered, transdermal application which can be especially useful for the management of facial wrinkles and hyperhidrosis.
➢ However, a topical formulation, if and when available, also has the potential orf overuse and misuse, if not administered carefully.
➢ Research is also being directed at modifications in the toxin molecule to change its duration of action and the target molecules. A reduced duration of action is desired for short term muscle weakening (e.g., healing of a post-traumatic wound). While a prolonged duration of action could be a huge advantage in conditions such as treatment of facial rhytids.

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