Chapter 10
Botulinum Toxin Therapy in Joint and Bone Problems – Emerging Literature Radiates Hope

Introduction

Botulinum neurotoxin (BoNT) is produced by a bacteria present in nature. It causes serious illness when it enters the human body in large amount through contaminated food. When used in medicine, the toxin is quantified in units, each unit reflecting certain degree and percentage of mortality among exposed mice. The contaminated food that causes illness in human usually contains hundreds of thousands or even millions of toxin units, whereas the amount used for medical treatment (through injection) is in most cases below 400 units.

The molecular structure of the botulinum toxin, history of its development as a therapeutic agent in medicine, and the different kinds of botulinum toxin are described in detail in the first three chapters of this book. In brief, of the 7 subtypes of the toxin, only types A and B are currently used in medicine due to their long duration of action. Three variants of the type A toxin are FDA approved under the trade names of Botox, Xeomin and Dysport, whereas only one type B toxin-Myobloc- is FDA approved. The toxin units are not exactly comparable, in clinical research, the following approximations are used:

Each 1unit of Botox = 1 Unit of Xeomin = 2.5–3 unit of Dysport = 40–50 units of Myobloc. For medical use, botulinum toxin is only used via injection either into the muscle or into/under the skin. Xeomin vials do not need refrigeration, whereas the other three toxins require refrigeration due to their heat sensitivity. Myobloc is provided as a prepared solution ready for injection, whereas, other the three type A toxins, need to be diluted with saline (salt water) before injection (see Chaps. 2 and 3 for details).

After injection, the carefully prepared and titrated toxin reaches the nerve ending and the region of nerve -muscle junction. It is in this junction that after entering the nerve ending the active moiety of the toxin -light chain (see Chap. 1) prevents release of certain chemicals which are essential for transmission of the nerve signal to the muscle and for muscle activation. In the sensory system botulinum toxin

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molecule blocks the function of sensory transmitters that relay the pain sensation to the brain. It is this effect over the pain transmitters that is of great interest in many medical disorders- inclusive of joint and bone disorders- in which the patients are afflicted by pain.

In his chapter, we will discuss the effect of botulinum toxin treatment on the pain associated with chronic osteoarthritis, tennis elbow, pain after total knee replacement and joint pain caused by imbalance of attached muscles.

Pain of Chronic Arthritis (Osteoarthritis)

The word arthritis describes inflammation of body joints. Each joint consist of two bones and a fluid filled space (synovia) in between the two, cartilages over the bone surfaces (hard and slick tissue), along with a joint capsule (synovial membrane). There are also ligaments, narrow bands of fibrous tissue that connects the bones together (Fig. 10.1). Except for the cartilages, all structures of the joint including the bones are richly supplied by pain sensing sensory nerves. In addition, in chronic conditions, a cascade of events leads to a phenomenon called sensitization in which many structures that have low pain threshold become sensitive to pain and

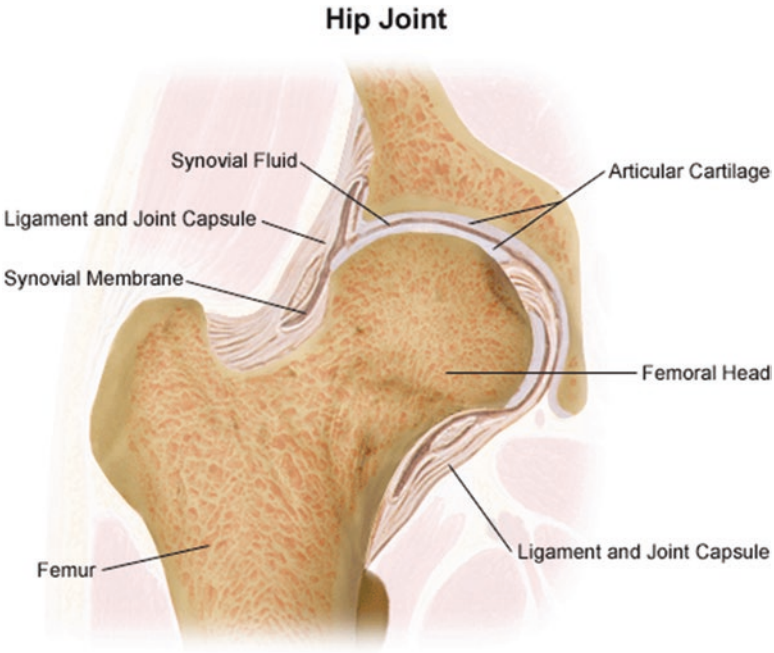

Fig. 10.1 Anatomy of hip joint – A thick synovial fluid is between the head of the long bone of the thigh (femur) and the adjacent pelvic bone, to facilitate movements of the joint. Courtesy of Oxford University Hospitals NHS Foundation Trust- UK

induce pain. Peripheral sensitization is a complicated phenomenon the details of which are beyond the scope of this chapter. In brief, changes in several chemicals known as pain transmitters and modulators enhances the sensitivity of peripheral nerve endings and spinal sensory cells to pain.

Osteoarthritis (inflammation of bone and joint) is the most common cause of pain among all pains involving the musculoskeletal (muscle and bone) system, affecting approximately 250 million people worldwide [1]. During life, 10–12% of all adults, experience osteoarthritic pain [2]. In the US, the number of patients with osteoarthritic pain is growing due to the aging population and effects of obesity. Osteoarthritis is among the leading causes of disability in elderly individuals [1]. The conditions that can be confused with osteoarthritis include trauma to the joint, pain due to ailment of muscles close to the joint and fibromyalgia, a diffuse painful muscle ailment associated with sleep disorder and dysfunction of glands.

Among body joints, the joints that are weight bearing such as hip and knee joints are most often affected by osteoarthritis. Over time and with age, the bones around the joint grow small bone spurs which irritate the nerves and the soft tissues around them. Gradually, local inflammation develops. Inflammation may affect the synovial membrane (Fig. 10.1) and gradually lead to accumulation of fluid in the joint (effusion). The involved joint becomes swollen and painful with pain getting worse during joint activity. In some patients, genetic predisposition attributes to the development of osteoarthritis.

The second most common form of arthritis is rheumatoid arthritis. Rheumatoid arthritis can be seen in many young individuals. Rheumatoid arthritis is a disease of the body's immune system leading to inflammation of the joint capsule with subsequent destruction of cartilage and bone Fig. 10.2.

Symptoms and signs of osteoarthritis include focal joint pain, joint stiffness, redness, joint swelling and limitation of joint movements. These symptoms increase with age and often lead to disability. Tests that are used for imaging the joints are useful in showing the extent of bone and cartilage damage. Among these tests, MRI is most accurate since it provides detail definition of bone and soft tissues.

Conventional treatment of arthritis includes multiple strategies. The results of these treatment strategies are usually modest and, in most patients, the level of pain relief is not satisfactory [1]. Medical treatment is often combined with physical therapy that includes exercises designed to improve the range of motion along with strengthening of the joints. Heat pads and ice packs may help to alleviate pain. In obese individual loss of weight is recommended. Massage of the affected joint, acupuncture and Yoga can also provide various degrees of pain relief.

Mild cases of osteoarthritis are treated by commonly used pain killers such as aspirin or Tylenol. The drugs that specifically target inflammation but are not in the steroid category such as motrin and advil are also frequently used for treatment of osteoarthritis. More severe cases require steroid therapy. Steroids can be taken orally (prednisone) or injected directly into the joint. Injection of hyaluronic acid into the joint has been shown to be helpful in some patients. This material which has a viscosity similar to synovia (joint fluid) coats the bone surfaces and prevents further bone damage.

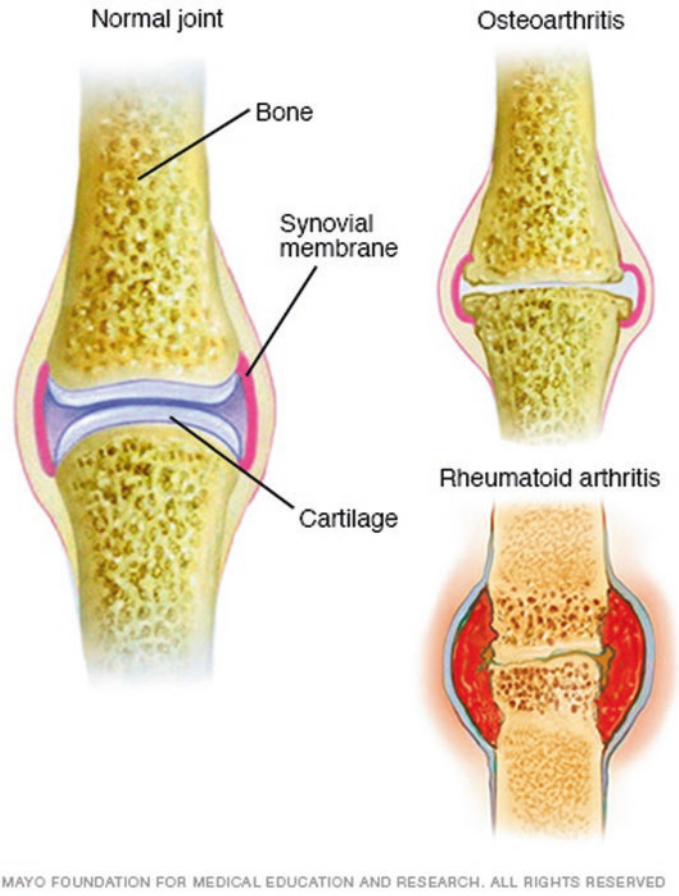

Fig. 10.2 Normal joint and joints affected by osteoarthritis and rheumatoid arthritis. Printed with permission from the Mayo foundation

Surgery includes joint fusion, repair and replacement. Joint fusion is used for smaller joints such as those of fingers and wrists. In the repairing procedure, the surgeon cuts across the bone above and below the joint, removes part of the bone and insert new bone in order to shift the weight away from the damaged part of the joint. For worn out joints, joint surfaces are replaced by metal or plastic parts.

Botulinum Toxin Therapy in Osteoarthritis (OA)

The modest effect of medical therapy in osteoarthritis, and reluctance of many patients with OA to have surgery, encouraged investigators to explore the efficacy of botulinum toxin injections for alleviation of pain in OA. As was discussed earlier,

animal studies have shown that injection of BoNTs into muscle inhibits release of pain transmitters from nerve endings and alleviates pain. Following the observation that Botox injected into dog's joints with arthritis relieves joint pain, researchers began to study its effect on human joints affected by osteoarthritis. Dr. Mahowald and his colleagues first reported that injection of Botox into the shoulder (100 units) or limb joints (25–50 units) can alleviate pain of arthritis in humans [3]. Other investigators subsequently found that injection of other type A toxins as well as B toxin into the human osteoarthritic joints can relieve this type of pain as well.

In a recent, high quality study, authors compared the effects of Botox with placebo (salt water) injection into the shoulder joints of 121 patients with OA. The study was blinded meaning neither the injecting doctor nor the patient knew what was injected (Botox or placebo). Half of the patients received Botox. The effect of injections was assessed by another doctor not involved in preparing the Botox or performing the injections. Standard scales for evaluation of joint pain, patients, quality of life and patients' degree of disability were used to assess the efficacy of the treatment over months of follow up after injections. The researchers found that Botox injection was statistically superior to placebo in regard to pain relief, improvement of quality of life and patient disability [4]. Botox and placebo groups had the same number of side effects which were all minor and self-limiting. The finding of this study are in agreement with the results of a recent review on the safety of BoNT injections in OA which has found no patient in all reported studies of BoNT therapy for OA reported any significant side effects after joint injections [5]. Using the criteria of the American Academy of Neurology (AAN), the level of efficacy of BoNT therapy for relieving pain of osteoarthritis is B (probably effective); this is based on availability of two high quality class II studies. The reader is referred to Chap. 3 of this book for definition of efficacy levels and class of the research studies (I, II, III, IV) based on the published guidelines of the AAN.

Tennis Elbow (Lateral Epicondylitis)

Rungue, in 1873, coined the term "tennis elbow" for a pain disorder which involves the elbow and causes an ailment in tennis players. It is believed that players with a strong back hand repeatedly traumatize the tendon of one of the extensor muscles of the wrist (short extensor) which is attached to the lowest part of the long bone of the arm called lateral epicondyle (Fig. 10.3). As a result of repeated trauma, multiple small tears develop in the tendon (where muscle attaches to the bone) and initiate pain.

Subsequent observations revealed that this form of muscle and bone injury is not limited to tennis players and a wide range of trauma to this region can cause it (weight lifting, certain jobs that require pulling and bending the elbow). Currently, the term lateral epicondylitis (LE) which means inflammation of lateral epicondyle (Fig. 10.3) is used more frequently in place of tennis elbow since the damaged

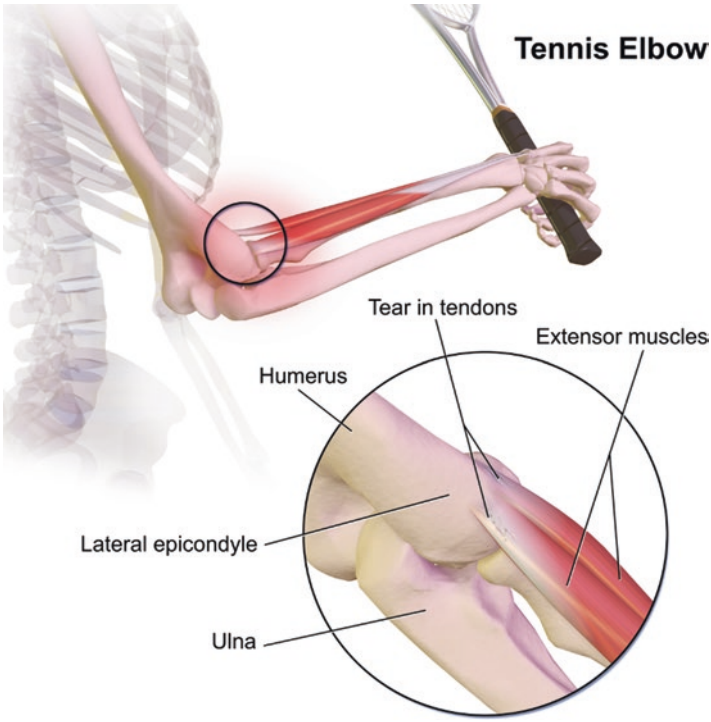

Fig. 10.3 Tennis elbow is caused by tears in the extensor wrist muscles close to lateral epicondyle of the elbow. From Wikemedia commons- licensed under creative commons attribution

muscle close to lateral epicondyle often manifests some degree of inflammation (accumulation of reactive blood cells in the issue).

Lateral epicondylitis involves 1 to 3% of general population over their life time. Men and women are equally affected with the age of onset being between 35–55 years. Most patients gradually recover from this condition over 6–24 months. In 5–10% of the patients, however, the condition continues and becomes the cause of chronic elbow and forearm pain [5]. Affected patients feel the pain in the area of the elbow with radiation to the forearm. In some patients with chronic pain, examination shows some limitation of wrist and finger movements. X-ray examination of the elbow shows local deposits of calcium in 25% of the patients. The MRI usually shows no significant bone or soft tissue pathology. For most patients, surgery is not necessary unless a serious pathology is suspected (tumor, infection, etc)

Several medical and non-medical approaches have been tried for management of pain in chronic LE. These include exercise therapy, taping the elbow, laser therapy, applying braces, acupuncture, and ultrasound therapy. Platelet-rich plasma injections is an expensive approach in which the patients' own blood is centrifuged and the buffer zone on the top (rich in platelets- blood cells which help to stop bleeding) is injected in the area of pain. The results of these strategies in chronic LE are at

best, modest, and consist of temporary pain relief. Furthermore, the lack of high quality studies makes it hard to discern the utility of these approaches. Local patches of glyceryl trinitrate have helped relieve pain in one high quality study (using placebo as control) but the results were temporary. In another high quality study, injection of hyaluronic acid gel into the joint, in a manner similar to that used in OA, reduced the patients' pain[6]. Injection of steroids (triamcinolone) into the joint has been used also for pain relief, but it has a high relapse rate. Different surgical approaches for management of LE associated pain have been used; some have succeeded to relieve the pain for 12 months.

Botulinum Toxin Treatment

Recognition of the pain killer effect of local botulinum toxin injection (now approved by FDA for treatment of migraine), encouraged investigators to study this mode of treatment for pain relief in LE. Over the past 15 years, more high quality studies (blinded, placebo controlled) have been performed using botulinum toxins in LE than any other mode of treatment for management of LE associated pain. Of 7 high quality studies published to date in this area, 4 blindly compare the effect of botulinum toxin with placebo and 3 compare the effect of botulinum toxin with steroids. In the placebo- controlled studies, authors used Dysport, a type A botulinum toxin, similar to Botox (see Chap. 3). Injections were performed either close to the painful epicondyle or a few centimeters lower into the short extensor muscle that is attached to the lateral epicondyle (Fig. 10.3). A total of 50–60 units of Dysport, roughly equivalent to 20–25 units of Botox, was used, and injected into 2 to 3 muscle sites. Among the four studies that compared the effect of Dysport with placebo, three have shown that BoNT therapy is clearly superior to placebo in reducing pain and improving the quality of life. In the comparator studies, both BoNT and steroid injections improved elbow and forearm pain. While the level of pain relief was initially higher in those patients who received steroids, patients who received BoNT injections demonstrated a more sustained pain relief which lasted 3–6 months. This data indicate that injection of botulinum toxin into the extensor muscle of the forearm close to the elbow is a reasonable alternative to surgery for management of intractable pain in chronic LE. A level B evidence level, probably effective (Using AAN's criteria- See Chap. 3), can be given to botulinum toxin therapy for relieving pain of tennis elbow based on the number of positive high quality studies. The drawback of botulinum toxin therapy for tennis elbow is development of weakness of finger extension that is seen in 30–40% of the patients after injection into the short extensor muscle of the forearm. Unfortunately, once developed, finger weakness can last up to 2–4 months. Future studies using smaller doses and more refined methods of botulinum toxin injection may overcome this unpleasant side effect.

Pain After Total Knee Replacement (Arthroplasty)

Advanced osteoarthritis of the knee which is associated with degeneration and destruction of the knee joint limits the patients' activity and may progress to total immobility. Total knee replacement - total knee arthroplasty (TKA)- is a common procedure for retaining the knee function. In 2010, the number of total knee replacements in the US was 719,000 [7]. It is estimated that over half of all patients with chronic knee osteoarthritis will undergo TKA. Modern knee replacement techniques using the latest and most advanced hard-wares have been very successful in improving the range of knee movements and improving patient's ambulation. Surgery is usually done under general anesthesia.; an alternative is spinal anesthesia which numbs the body below the waist. With spinal anesthesia, the patient has the option to remain conscious during the operation.

Unfortunately, 10–34% of the patients develop chronic knee pain after total knee arthroplasty that greatly impairs their quality of life. The pain can be a newly developed pain or an enhancement of the pain that the patient experienced before surgery [8]. A number of factors have been associated with development or exaggeration of knee pain after total knee surgery; these factors include having a high level of pain before surgery, presence of other painful muscle or joint disorders and poor mental condition of the patient [9].

Management of sustained pain after total knee arthroplasty consists of physical therapy, stretch exercises and use of pain killers. Steroid injection into the soft tissue and around the painful knee joint has been reported to relieve pain in some patients. However, all studies are open label (no placebo for comparison) and, hence, the results are colored by a moderate to high degree of bias.

Botulinum Toxin Therapy

Dr. Singh and his colleagues conducted a high quality study on 49 patients among whom, 60 knees had total arthroplasty [10]. Thirty legs received 100 units of Botox, diluted in 5 ccs of saline injected into the knee joint, whereas the other 30 legs received 5 cc of saline (salt water, placebo) only while using the same methodology. The patients' mean age was 67 years. In the Botox group, 22% of the patients were female. Patients' response was evaluated by several outcome measures among them three scales designed specifically to assess pain. A WOMAC scale (western Ontario McMaster Universities osteoarthritis index) was also used to assess functionality, joint stiffness and pain. Patients were followed for 6 months after a single set of injections.

At two months, the WOMAC osteoarthritis scale showed significant improvement of all three of its subsets (pain, functionality and stiffness) in patients who received Botox injections but not in the placebo group. There was also a marked difference between the Botox group and the saline group in regard to response to

pain in the pain specific scales. A notable pain relief was noted in 71% of the patients who had received Botox injections versus 35% in the placebo group. Side effects were minor, consisting of transient local pain after injection and occurred with comparable frequency between the two groups (Botox and placebo). This positive, high quality class II study (see Chap. 3 for class definition) indicates that Botox injection into the knee joint is possibly effective to relieve recalcitrant pain of total knee arthroplasty. Botox injection into the knee joint may be tried when other management strategies fail to relieve this form of pain.

Chronic Knee Pain due to Imbalance of Vastus Muscles

A common cause of chronic knee pain is poor balance between the activity of lateral and medial muscles of the thigh (vastus muscles). Vastus muscles along with rectus muscle extend the knee.

Over activity of the lateral vastus muscle (vastus lateralis) or/and delayed activity of medial vastus muscle leads to misalignment of the patella (knee's funny bone) and causes chronic pain in front of the knee (Fig. 10.4). The patella gradually shifts laterally and tilts. The pain is felt in the front of the patella and is provoked by ascending or descending stairs, kneeling, squatting and prolonged sitting [11]. It is a debilitating condition which is more common among young women. This condition is also called

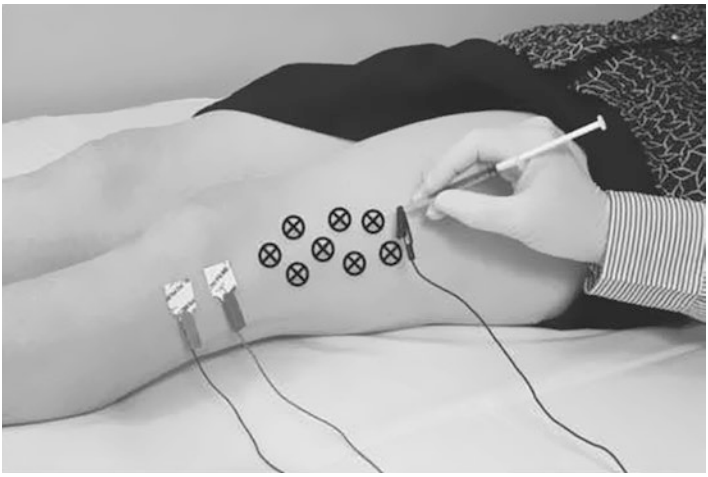

Fig. 10.4 Method of botulinum toxin injection used by Singer and co-workers for treatment of vastus lateralis imbalance. Reproduced with permission from the BMJ Publishing group. The injecting syringe is connected to an EMG needle that identifies the muscle via the sound of its electrical activity. A total dose of 500 units of Dysport is injected into eight sites (designated by Xs) into the vastus lateralis muscle

patello-femoral syndrome (PFS). In 2008, the number of patients affected by the PFS was estimated as 971,000 costing the U.S. economy $8.3 billion (www.pearldiverinc.com).

Imaging of the knee joint (X-ray/MRI) usually do not show any abnormality. The goal of treatment is to reduce pain and swelling, improve the balance between vastus medialis and vastus lateralis muscles, restore normal gait, and improve postural control of the lower extremity. Short -term taping of the patella associated with special exercises to strengthen the thigh muscles provides partial pain relief. Many patients use common pain killers with degrees of success. Surgery is hardly indicated. High quality studies are not available to compare different methods of treatment in PF syndrome.

Botulinum Toxin Treatment of VLS

In 2010, Dr. Singer and his colleagues reported on the results of a study that compared injection of Dysport (a botulinum toxin type A) with placebo (salt water) in 24 patients with vastus lateralis(VL) imbalance (PFS) [12]. In the toxin group, 500 units of Dysport (roughly equal to 200 units of Botox) was injected at 8 points into the VL muscle (Fig. 10.4). The same injection methodology was used for the saline group. The pain and functionality was evaluated through standard scales, blindly, at 3 months. Patients who received Dysport injections showed significant improvement in walking, stair climbing and squatting, whereas those who received placebo did not. Furthermore, there was a marked reduction of knee pain on the visual analogue scale, a 0–10 level of pain reported by the patient. There was no significant side effects after Dysport injections. This high quality study, rated class II, suggests that botulinum toxin injection into vastus lateralis muscle is helpful in relieving pain and improving functionality of patients with PFS. The dose of Dysport used in this study was safe and did not produce significant muscle weakness or any other unwanted side effects.

Conclusion

Botulinum toxin injection into the joint effectively improves pain of chronic osteoarthritis as well as chronic knee pain after total knee replacement surgery (arthroplasty). Injection of Botulinum toxin into the lateral muscle of the thigh (vastus lateralis) corrects the imbalance between lateral and medial thigh muscles via decreasing the tone of this muscle and consequently relieves the chronic knee pain at the region of the patella (front of the knee). High quality studies have shown that botulinum toxins therapy for these indications (with applied doses) is safe and well tolerated by the patients.

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