Chapter 12
The Role of Botulinum Toxin Therapy in Joint and Bone Problems

Abstract Animal studies have shown that local injection of botulinum toxins improves pain behavior via blocking the release of pain transmitters and modulators. In human, carefully designed studies comparing the effect of local injection of botulinum toxins with placebo (salt water) have demonstrated efficacy of toxin injection in relieving the pain of chronic osteoarthritis, local pain of tennis elbow, chronic pain after knee surgery and knee pain related to tightness of lateral thigh muscles.

Keywords Botulinum toxin · Botulinum neurotoxin · Tennis elbow · Lateral epicondylitis osteoarthritis · Pain after knee surgery · Patellofemoral syndrome

Introduction

Botulinum neurotoxin (BoNT) is produced by a bacteria present in nature. It causes serious illness when it enters the human body in large amounts through contaminated food. When used as a 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 9 subtypes of the toxin, only types A and B are currently used in medicine due to their long duration of action. Five type A toxin are FDA approved under the trade names of Botox, Xeomin, Dysport, Jeuveau and Dyxxify whereas only one type B toxin—Myobloc—is FDA approved. Jeuveau is currently approved only for cosmetic use. The toxin units for different toxin types are not exactly comparable. However, in research and in medical practice, the following approximations are often used: Each

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1unit of Botox = 1 unit of Xeomin = 2.5–3 units 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. Details of different botulinum toxin preparations, their need for refrigeration and their unit differences are discussed in Chap. 3 of this book. After injection, the carefully prepared and titrated toxin reaches the nerve ending and the region of nerve -muscle junction. It is at this junction that after entering the nerve ending the active moiety of the toxin—its light chain (see Chap. 2 for botulinum toxin structure)—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 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 therapy on 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; cartilage (hard and slick tissue), over the bone surfaces, along with a joint capsule (synovial membrane). There are also ligaments, narrow bands of fibrous tissue that connect the bones together (Fig. 12.1). Except for the cartilages, all structures of the joint including the

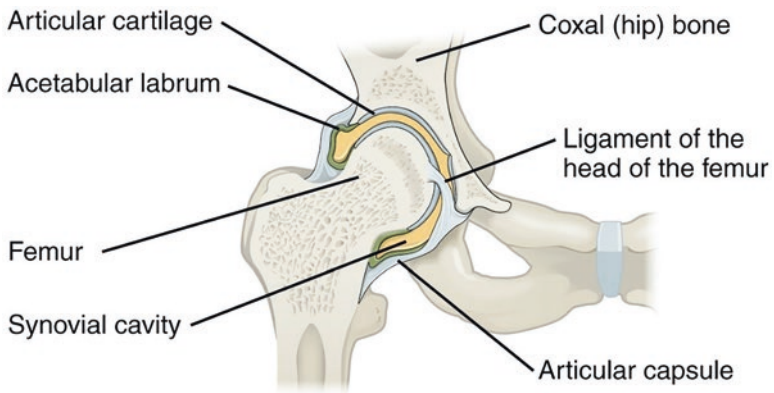

Fig. 12.1 Anatomy of hip joint—A thick synovial fluid is between the head of the long bone of the thigh (femur) and the adjacent pelvic bone, to facilitate movements of the hip joint. (Courtesy of WikiMSK. Permission to reuse is granted under Creative Commons Attribution-ShareAlike (CC-BY-SA-4.0) license)

bones are richly supplied by sensory nerves that sense pain. 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 induce pain. Peripheral sensitization (PS) 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 enhance the sensitivity of peripheral nerve endings to pain signals. Continued PS leads to central sensitization (CS) of spinal cord nerve cells leading to pain chronicity.

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 fatigue and sleep disorder.

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. 12.1) 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. 12.2).

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 visualizing the joints are useful in showing the extent of bone and cartilage damage. Among these tests, MRI is most accurate since it provides detailed definition of the 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 individuals, 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 [3]. Steroids can be taken

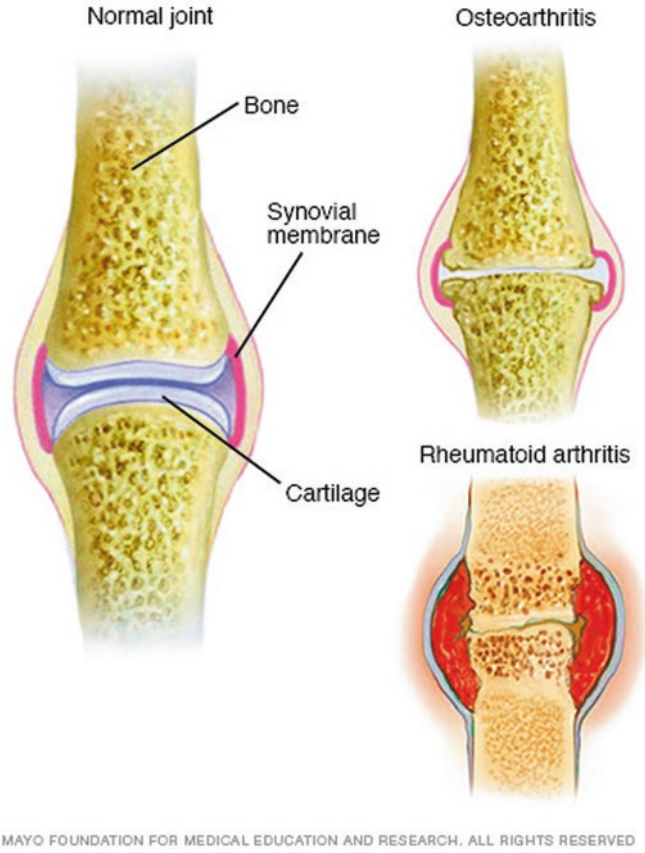

Fig. 12.2 Normal joint and joints affected by osteoarthritis and rheumatoid arthritis. (Courtesy of Mayo foundation)

orally (prednisone) or injected directly into the joint. Their chronic use, however, may damage the cartilage and enhance progression of osteoarthritis. 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 may prevent further bone damage.

For the past few years, several new material have been tried for treatment of osteoarthritis including cytokine inhibitors, platelet-enriched plasma, aspirates from bone marrow, insertion of fatty material inside the joint (adipose tissue) or so called expanded mesenchymal stromal cells (MSC); none have been found to have clinically relevant long-term effects [4].

Surgery includes joint fusion, repair and replacement. Joint fusion is used for smaller joints such as those of fingers and wrists. During the 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 or skin inhibits release of pain transmitters from nerve endings and alleviates pain [5–7].

Following the observation that Botox injected into dog's arthritic joints relieves joint pain [8], researchers began to study its effect on human joints affected by osteoarthritis. In 2006, 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 [9]. Another study, published in 2010, compared the effect of Botox versus placebo and found Botox to be superior to placebo (saline injection) in 60 patients with knee osteoarthritis [10]. In a recent, high quality, larger study authors compared the effects of Botox with placebo (salt water) injection into the knee 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 [11]. 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. This review [12] found no patient in any of studies on BoNT therapy for OA with any significant side effects after joint injections. Subsequently, several other studies also showed that injection of different type A botulinum toxins, Botox or Dysport into the knee joint of patients with OA can relieve joint pain [13–15].

These positive results were contradicted by a more recent study (blinded and placebo-controlled) of 158 patients that found both botulinum toxin and placebo (salt water-saline) injections into the knee joints of patients with knee arthritis produced the same degree of pain improvement [16]. There are, however, two issues with this study: 1- the pain scale used in this study was not validated for use in knee osteoarthritis, 2- most patients in the placebo arm of the study improved with the injection of salt water. Whenever the placebo has the exact effect as the study's drug, the studied population is suspect to be unusually sensitive to placebo effect invalidating the observation.

Over the past 10 years, several comparative studies have compared the effect of intra-articular (IA) injection of botulinum toxins with other agents that are commonly used for relieving the symptoms (mostly pain) of osteoarthritis. In a study of 30 patients with advanced osteoarthritis of the knee, investigators found that combined injection of Botox with triamcinolone(a potent steroid) was significantly

superior in pain relief compared to triamcinolone alone over 6 weeks to 6 month post-injection period [17]. In another study [18], IA injection of botulinum toxin plus exercise was found to be superior to IA injection of hyaluronate, a compound that is frequently used for achieving symptom relief in knee OA. Yet in another study, IA injection of a triamcinolone was compared with IA injection of 100 units of Botox in patients with knee OA [19]. Both injections were equally effective on pain at 12 weeks, but authors found injection of the steroid offered more pain relief at 4 weeks. In this study, the injected dose of Botox however, was 100 units, less than 200–300 units used in most studies of knee arthritis. Moreover, chronic and repeated steroid injections may lead to cartilage degeneration, bone damage or unwanted metabolic changes, not seen with IA injection of botulinum toxins. Most recently, an extensive review of this subject including 7 studies and 548 patients with application of advanced statistical methods (meta-analysis) concluded that IA injection of botulinum toxins is effective in relieving pain of knee osteoarthritis [20]. The authors encouraged the need for conduction of more high quality (double-blind, placebo-controlled) studies.

Much less research has been done on the role of IA injection of botulinum toxin for relieving distressing symptoms of OA in other joints (shoulder, hip, ankle). One study, cited earlier in this chapter, reported improvement of pain and function after IA injection of Botox in 9 shoulder joints [9]. A recent systematic review of IA injections for ankle osteoarthritis concluded that the limited data on the currently studied compounds (botulinum toxin, hyaluronate, plasma-rich protein) do not support evidence for a clinically relevant improvement of symptoms [21]. On hip osteoarthritis, preliminary data from two open label (not placebo- controlled) studies suggest improvement of pain after injection of 400 units of Dysport [22] into the hip joint or into the adductor muscles of the thigh (large muscles that bring the hips together) [23]. Dysport is another botulinum toxin type A; each 2.5–3 units of Dysport approximates 1 unit of Botox. For defining the role of botulinum toxins in hip osteoarthritis, data from blinded and placebo-controlled studies are needed.

Tennis Elbow (Lateral Epicondylitis- LE)

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/ extensor brevis) which is attached to the lowest part of the long bone of the arm called lateral epicondyle (Fig. 12.3). As a result of repeated trauma, multiple small tears develop in the tendon (where muscle attaches to the bone) causing pain at the elbow region. Pathological evaluation of the involved tendon often shows presence of mild inflammation.

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 such as weight lifting or certain jobs that require repetitive pulling and bending of the

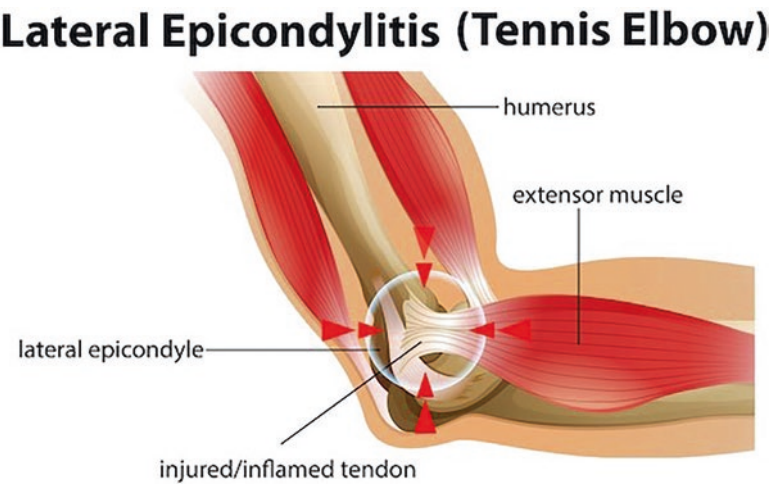

Fig. 12.3 Tennis elbow is caused by tears in the extensor wrist muscles close to lateral epicondyle of the elbow. (Figure designed by Free Pik)

elbow can cause the same problem. It is believed that laborers lifting weights in excess of 20 kg, more than 10 times per day can develop tear (s) in the tendon leading to LE [24]. Currently, the term lateral epicondylitis (LE) which means inflammation of lateral epicondyle (Fig. 12.3) is used more frequently instead of tennis elbow since the damaged muscle close to lateral epicondyle often manifests some degree of inflammation (accumulation of reactive blood cells in the issue). However, this term has also been challenged since inflammatory finding are subtle and may not explain the severity of symptoms (pain and limitation of elbow function). More recently, the term lateral epicondylosis (disease or dysfunction of lateral epicondyle) is preferred by some investigators [24].

Lateral epicondylitis (epicondylosis) affects 1–3% of general population over their life time. Men and women are equally affected with the age of onset being between 35 and 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 [25]. 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. In chronic cases, 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 the pain in chronic LE. These include exercise therapy, physiotherapy, taping the elbow, bracing, 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 to relieve pain in patients with LE according to high quality studies (using placebo as control), but the results are temporary [26]. Among non-steroidal analgesics, diclofenac was shown to improve pain of LE better than naproxen [24]. Injection of hyaluronic acid into the joint, in a manner similar to that used in OA, has been reported to reduce the elbow pain in patients affected by LE [27], but the effect is also short lived [28]. In severe cases, injection of steroids (triamcinolone) into the joint for pain relief has been used with temporary success in LE, but it has a high incidence of relapse. Furthermore, repeated injection of steroids can cause unwanted bone degeneration and metabolic abnormalities.

Surgery is reserved for patients who have failed medical treatment and is performed in less than 10% of the patients [29]. Three different surgical approaches are employed to alleviate the symptoms of LE. These include open surgery, percutaneous surgery and arthroscopic surgery. In arthroscopic surgery debridement of the damaged tendon is performed via an instrument (arthroscope) without widely opening the area. Follow up studies of large number of patients have shown comparable results for all three surgical approaches in management of LE [30, 31]. Cohen and co-workers have found, however, that the time to return to work was twice longer in patients that underwent open surgery compared to those who had arthroscopic surgery (mean 66 days versus 35 days) [29].

Botulinum Toxin Treatment of Tennis Elbow (LE)

Recognition of the pain killer potential 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 20 years, several studies have been published on the efficacy of botulinum toxin injections in alleviating LE symptoms. Among them, five could be classified as high quality since they blindly compared the effect of the botulinum toxin injection with placebo (salt water injection) in LE. One of these studies used Botox [32], whereas the other four used Dysport [33–36]. As indicated earlier, Dysport is a type A botulinum toxin similar to Botox (see Chap. 3 for details). Injections were performed either close to the painful epicondyle or a few centimeters lower into the short wrist extensor muscle that is attached to the lateral epicondyle (Fig. 12.3). The Botox study used a total of 60 units, whereas in the four Dysport studies, the authors used 50–60 units, roughly equivalent to 20–25 units of Botox. Each patient received 2–3 injections either close to the elbow or a down the forearm over the short extensor tendon. Among the five studies that compared the effect of Dysport or Botox with placebo, four have shown that BoNT therapy is clearly superior to placebo in reducing pain and improving the quality of life in patients with LE. The one study that did not show improvement of

LE after botulinum toxin injection [34] assessed the pain only once, 3 months after injection. This may explain the negative result of the study since by 3 months, most of the effect of botulinum toxins is usually vanished (4 and 8 weeks assessment are much more accurate).

The optimum location of the injection (at the area of epicondyle or down the forearm into the short extensor muscle) and the optimum dose of the toxin (low dose versus high dose) have been studied, recently. In one review of the literature [37], researchers have found that toxin's injection into the wrist extensor muscle at a point(s) 1/3 of the length of forearm down from the involved epicondyle was more effective than injection at or close to involved epicondyle. In another study, both low dose (10 units) and high dose (50 units) of Medytoxin (Korean toxin with units close to Botox) were effective, but the higher dose of 50 units better alleviated the patients' symptoms (pain and limitation of arm movement) [38].

Several investigators compared the effect of Botulinum toxin injection in LE with other commonly used injectable substances (steroids, hyaluronic acid, etc.). These studies showed that the two most effective treatments were injection of botulinum toxin type A (Botox or Dysport) or steroids (triamcinolone) [39–41]. Steroid and botulinum toxin therapy had comparable efficacy in alleviating the symptoms of LE, though in one review steroids were found to have better analgesic effect over the initial 4 weeks after injection [41]. Botulinum toxin injection is probably less painful than steroid therapy since it is performed with a thin and short needle. Furthermore, repeated injection of botulinum toxin has less side effects than steroid therapy (see steroid side effects described earlier in this chapter). Weakness of middle finger extension is a common side effect of botulinum toxin therapy in LE (30–40%) which may last for several weeks. Future studies using smaller doses and more refined methods of botulinum toxin injection may overcome this 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 [42]. 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 hardware's have been very successful in improving both the range of knee movements and patients' 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 TKA 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 [43]. 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 [44].

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

Botulinum Toxin Therapy for Pain Following Total Knee Replacement

In 2010, Dr. Singh and his colleagues published the results of a high quality study on 49 patients among whom, 60 knees had total arthroplasty [45]. 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. The patients' mean age was 67 years. Patients' response was evaluated by several outcome measures among them scales designed specifically to assess pain. A WOMAC scale (western Ontario and 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 2 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—a finding that was statistically significant. Side effects were minor, consisting of transient local pain after injection and occurred with comparable frequency between the two groups (Botox and placebo).

A sizeable number of patients after TKA surgery gradually develop progressive increased tone in the muscles that flex the knee (hamstring muscle—the large muscle located in the back of the thigh) leading to forced flexion of the knee and difficulty in walking. Progressive stiffness of this muscle can lead to loss of elasticity with replacement of some of the muscle fibers by non-elastic fibrous tissue, referred to as contracture. Injection of botulinum toxin A into the flexor muscles of the knee (hamstrings) decreases the muscle tone and prevents severe and disabling contractures (stiff muscle, lost volume and elasticity) [46, 47]. In a high quality study (double-blind, placebo-controlled), patients who received 50 units of Botox into each hamstring muscle demonstrated significant improvement of flexion contracture along with 18° improvement in knee extension [47].

Chronic Knee Pain Due to Imbalance of Vastus Muscles (Patellofemoral Syndrome-PFS)

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 the rectus muscles (located in front of the thigh) extend the knee.

Overactivity of the lateral vastus muscle (vastus lateralis-VL) or/and delayed activity of medial vastus muscle (VM) leads to misalignment of the patella (knee cap bone) and causes chronic pain in front of the knee. The knee cap 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 [48, 49]. Patellofemoral syndrome (PFS) has an incidence of 9.2% [49] and is twice more common among women especially, especially young women and those engaging in sports (running, tennis, etc.).

Imaging of the knee joint by ultrasound or MRI may show displacement of the patella. 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. Treatment is difficult. Short -term taping/bracing of the patella associated with special exercises to strengthen the thigh muscles provides partial pain relief. Many patients rely on commonly used pain killers with modest degrees of success. Surgery is usually not indicated. High quality studies are not available to compare different methods of treatment in PFS syndrome.

Botulinum Toxin Treatment of Pain Associated with PFS

In 2011, 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) [50]. Vastus lateralis is a large muscle located on the lateral part of the thigh that extended lower leg below the knee. The toxin injected group received 500 units of Dysport (roughly equal to 200 units of Botox) at 8 points into the VL muscle (Fig. 12.4). The same injection method was used for the saline (placebo) group. The pain and leg function 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 (VAS), a scale that measures pain at 0–10 levels, reported by the patient. There was no significant side effects after Dysport injections.

This observation was supported by subsequent open label (not blinded) studies [51, 52]. In the most recently published study on this subject [52], Pal and coworkers investigated the effect of botulinum toxin injection in both vastus lateralis

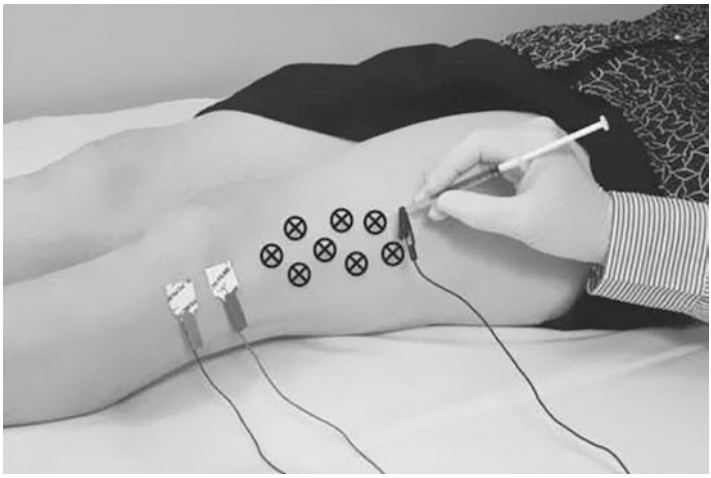

Fig. 12.4 Method of botulinum toxin injection used by Singer and co-workers for treatment of vastus lateralis imbalance. From Singer et al. [50]. The injecting syringe is connected to an EMG needle that identifies the muscle via the sound of its electrical activity. A total dose of 500 units of Dysport is injected into eight sites (marked by Xs) into the vastus lateralis muscle. Courtesy of BMJ Publishing group. Licensed under. (http://creativecommons.org/licenses/by/4.0/)

muscles in 13 patients with PFS. Patients' main complaint was pain in the area of knee cap. Patients' position of the knee cap and degree of their patellar tilt was documented by CT scan. The type of toxin, method of injection and the toxin dose was identical to that used by Singer et al. [50]. Botulinum toxin was injected on both sides and into the most distal part of the lateral rectus muscles (close to the knee). Patients' response to pain and their leg function were measured by standard scales. Botulinum injection was combined with special home exercises designed to strengthen the vastus lateralis muscles. This combination therapy improved patellar tilt and patellar angle; it also markedly reduced the patients' pain at the patellar and lateral thigh region. Patients' pain reduction continued over a follow up period of 2 years.

Conclusion

Botulinum toxin injection into the joint effectively improves pain of chronic knee osteoarthritis as well as chronic knee pain after total knee replacement surgery (arthroplasty). There is limited evidence that this treatment approach may improve pain of hip and shoulder osteoarthritis. High quality studies indicate that botulinum toxin injection close to the elbow can improve persistent pain at the region of the elbow in lateral epicondylitis (Tennis elbow). Botulinum toxin injection into the knee joint improves persistent pain in the knee region experience by some patients after total knee replacement. Injection of Botulinum toxin into the lateral muscle of

the thigh (vastus lateralis) corrects the imbalance between lateral and medial thigh muscles in patellofemoral syndrome (PFS) via decreasing the tone of this muscle, consequently relieving the chronic knee pain at the region of the knee cap (patella). Evidence from the literature indicates that with the reported doses applied for these indications, botulinum toxins therapy is safe and well tolerated by the patients.

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