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RESEARCH ARTICLE

Methods of hamstring muscle injection of botulinum toxin type A combined with periarticular injection after total knee arthroplasty

Xiaofeng Jiang†, TaoTao Jiang†, Xiaojun Qi, Pengzhou Gai, Hongliang Sun and Guangda Wang*

Department of Joint Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, 20 Yuhuangding East Road, Yantai, Shandong Province 264000, China

Abstract

This study aimed to report on a method for injecting botulinum toxin type A into the hamstring muscles combined with periarticular injection in total knee arthroplasty (TKA) patients. We enrolled patients who underwent elective unilateral TKA at our hospital from February 2021 to December 2021 and administered botulinum toxin type A hamstring muscle injection combined with periarticular injection. We established and reported a detailed method for this combined approach, which could provide an alternative analgesic regimen after TKA in clinical practice.

Keywords: *total knee arthroplasty*; *botulinum toxin type A*; *hamstring injection*; *analgesia*

Received: 23 February 2023; Accepted: 27 February 2023; Published: 03 April 2023

Total knee arthroplasty (TKA) is an increasingly common surgical intervention to relieve pain and improve physical dysfunction associated with end-stage degenerative joint disease (1, 2). For most total knee replacement patients, severe pain after TKA is both a fear and a torture. Poor pain control after TKA can significantly increase the incidence of perioperative complications (3), and affect the long-term prognosis of patients. Optimal postoperative analgesia after TKA should help reduce the incidence of perioperative complications and adverse reactions. For TKA patients, satisfactory postoperative analgesia should be their best goal. Pain management strategies have evolved over the past few decades (4), from intramuscular anesthesia injections in the 1980s, patient-controlled intravenous analgesia in the 1990s, and peripheral nerve block analgesia in the early 21st century to the most recent ones, periarticular injections of complex multimodal analgesia being prevalent. Currently, most pain management protocols continue to use a multimodal analgesic regimen of oral medications, motor-sparing selective nerve blocks (e.g. adductor canal blocks), and periarticular injections. Ultimately, the ideal analgesic regimen after TKA should effectively relieve postoperative pain, avoid side effects of analgesic drugs, and promote early functional recovery of patients.

This study reports the method of hamstring muscle injection of botulinum toxin type A combined with periarticular injection for TKA analgesia.

Methods and materials

Research subjects

Five patients with primary unilateral knee osteoarthritis (KOA) who met the indications for surgery in the Department of Joint Orthopedics from February 2021 to December 2021 were enrolled from Yantai Yuhuangding Hospital in Shandong Province. The patients included 2 males and 3 females aged 57–61 years. After being reviewed and approved by the Ethics Committee of Yantai Yuhuangding Hospital (#2020.303), and after actively communicating with the patients and their families participating in this experiment, they agreed to sign the informed written consent.

†Contributed equally to this paper.

Drugs and equipment

The study included the following drugs and equipment: botulinum toxin type A (Lanzhou Biotechnology Development Co., Ltd., 50 units/bottle, diluted with normal saline to 1 ml), a cocktail (recipe: 150 mg ropivacaine + 1 mg triamcinolone acetonide + 10 mg morphine, diluted with normal saline to 60 ml), an American Zimmer artificial surface posterior stabilized prosthesis (Nexgen-LPS high flexion), a 400 ml negative pressure drainage bottle, tranexamic acid injection, and a knee replacement device.

Diagnostic criteria

The diagnosis of KOA was based on published standards (5), which included: 1) Knee joint pain that has not been relieved in the past month; 2) Age ≥ 50 years old; 3) Standing X-ray films showing narrow joint space, osteophyte formation, subchondral bone sclerosis, and/or cystic degeneration (Fig. 1A); 4) Morning stiffness time ≤ 30 min; 5) Movable joints with bone friction (sound). The diagnosis of KOA can be made if any two of the above items are present.

Knee osteoarthritis can be classified into five grades according to Kellgren-Lawrence radiology criteria: Grade 0 indicates no change (normal); Grade I indicates possible gap narrowing and osteophytes; Grade II indicates narrowing of the gap and a small amount of osteophytes; Grade III indicates a clearly narrowed space, mild bone sclerosis, and a moderate amount of osteophytes; Grade IV indicates a significantly narrowed gap, severe bone sclerosis, a large number of osteophytes, and obvious bony deformity. According to the degree of the lesion, the radiological classification is further divided into three stages: early stage (grades 0 and I), middle stage (grades II and III), and late stage (grade IV).

Inclusion criteria

Inclusion criteria included: 1) meeting the new diagnostic criteria for KOA; 2) having middle to advanced radiological lesions; 3) having primary unilateral KOA; 4) undergoing unilateral TKA for the first time; 5) receiving neuraxial anesthesia; 6) having knee joint contracture between 10° and 20° (Fig. 1B); and 7) having obvious indications for TKA surgery.

Exclusion criteria

Exclusion criteria included the following: 1) Failure to meet the above inclusion criteria; 2) Age less than 55 years or greater than 65 years; 3) Body mass index (BMI) greater than 30 or less than 20; 4) Abnormal coagulation function; 5) Inability to communicate normally or a history of taking psychotropic drugs; 6) Systemic or local infection; 7) History of allergy to anesthesia and other drugs; 8) Central or peripheral neuropathy; 9) Presence of other serious diseases; 10) Failure to comply with the relevant requirements of the experiment, and inability to cooperate with the completion of rehabilitation.

Results

Preparation

The anesthesia grade of the patients was I–II. The operations were all performed by the same chief physician. Food and drink were routinely fasted before the operation, Celebrex was taken orally for preemptive analgesia, and cephalosporin antibiotics were used 30 min before the operation to prevent infection.

Anesthesia and disinfection

The patient's information was checked, and electrocardiogram (ECG) was monitored. The anesthetist was required to perform anesthesia in the same manner, i.e. selecting the level of the anterior superior iliac spine (around L3–4) in the lateral position. Lidocaine hydrochloride intraspinal anesthesia was administered with local anesthesia infiltration, and the anesthesia level was maintained at T8–10. After administering anesthesia, the patients were placed in a supine position, and gypsum cotton was applied to the proximal femur, followed by tying a tourniquet. Disinfection was performed from the bottom of the tourniquet to the sole of the foot. The blood-expelling belt was wrapped from the distal end up to the knee joint.

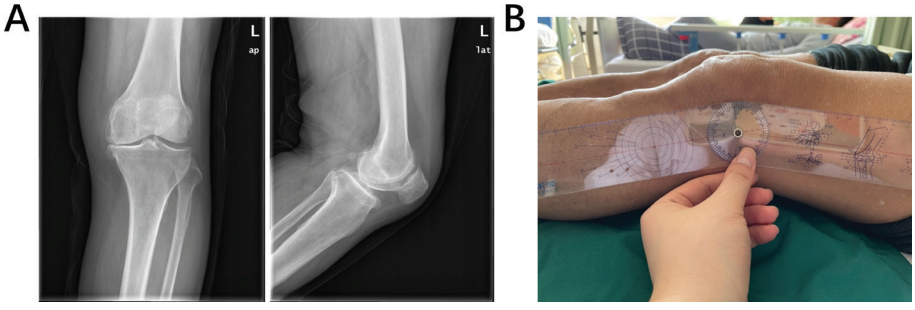

Fig. 1. (A) Preoperative anteroposterior and lateral radiographs of knee joint. (B) Flexion contracture of the knee.

Surgical procedures

The choice of surgical approach can fully expose the surgical field. The medial parapatellar approach through a median incision of the knee joint was routinely used. After the skin was cut to separate the subcutaneous fascia and other tissues, bleeding was stopped with an electric knife. The joint capsule was then opened, and the patella was pulled outward with a Hoffmann retractor. The bone and cartilage surfaces were exposed, and part of the soft tissue and anterior osteophyte were resected.

Treatment of the distal femur: Open the intercondylar fossa, insert the intramedullary positioning guide, fix the steel nail, and perform the osteotomy with a swing saw. Measure the size of the femur, install the multidirectional osteotomy plate for the femoral condyle, perform multidirectional osteotomy on both sides of the condyle, and perform subperiosteal dissection of the posterior joint capsule to reconstruct the articular fovea of the posterior femur.

Proximal tibial treatment: Insert the Hoffmann retractor into the rear of the tibial plateau. Press down to push the tibia forward, and use the locator to adjust the retroversion. Determine the tibial force line, fix the tibial guide for osteotomy, and pay attention to protecting the medial and lateral collateral ligaments and the posterior joint capsule. Measure the tibial plateau model.

Soft tissue balance: Through soft tissue loosening, blunt periosteum peeling, and other methods, the inner and outer space of the knee joint and the flexion and extension space can be balanced.

Patella treatment: According to the prosthesis, the patella was properly trimmed until it fit within the movement track, and the nerve was denervated using an electric knife to protect the patellar ligament.

As for the release of knee flexion contracture, the following procedures are performed uniformly during the operation: equal volume osteotomy, soft tissue release, posterior joint capsule release, removal of posterior joint capsule osteophytes, and balancing of flexion and extension gaps.

Femoral and tibial molds are placed and corresponding spacers are embedded in the trial mold. The overall stability of the knee joint is evaluated again, and the trial mold is removed after satisfaction.

Take appropriate bone pieces to fill the opening of the femur. Spray the femur and tibia fully with a pulse gun and, at the same time, quickly stir the bone cement for later use. Both the control group and the experimental group injected the prepared 20 ml cocktail with a syringe into the posterior joint capsule of the knee joint, including surrounding tissues such as the medial and lateral collateral ligaments (Fig. 2A). On the basis of this, the experimental group injected botulinum toxin type A into the hamstring muscles, including semitendinosus, semimembranosus, and biceps femoris, in the posterior joint capsule. These are the posterior muscle groups of the thigh, which can extend the hip joint and flex the knee joint. They mainly prevent excessive forward movement of the tibia and stabilize the knee joint. The operation involves using a syringe to puncture the posterior hamstring muscle, mainly semimembranosus, through the posterior joint capsule. The syringe is withdrawn without blood reflux, and BoNT/A 1 ml is injected at multiple points. The control group is injected with 0.9% normal saline 1 ml into the hamstring muscle in the same way. The prosthesis with bone cement is installed, and the knee joint is kept in a straight position until the bone cement and the prosthesis are squeezed and fixed. The overflowing bone cement is trimmed, and the pulse gun is used to thoroughly irrigate the entire joint cavity. Multi-point injection of 20 ml of cocktail is performed around the joint capsule and subcutaneous soft tissue in both the control group and the experimental group. The drainage tube is punctured on the upper lateral side, avoiding the lateral collateral ligament, and the incision is closed. Intravenous tranexamic acid is administered before loosening the tourniquet. Both the control group and the experimental group are given 20 ml of tranexamic acid, poured into the joint cavity. After checking the tightness of the 400 ml negative pressure drainage bottle, the drainage tube is connected to the surgical sheet, and the itinerant nurse slowly releases the tourniquet. Electrocardiogram monitoring is observed, and the patient is returned to the ward after their vital signs are stable. The patient is then continuously monitored and given oxygen inhalation, systemic treatments such as preventing infection, reducing swelling, relieving pain, rehydration, etc. Attention is paid to observe the changes in the patient's condition.

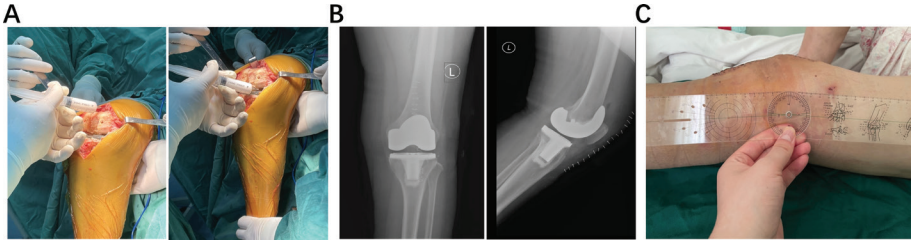

Fig. 2. (A) Cocktail injection of tissue around the joint cavity. (B) Frontal and lateral of knee X-ray after total knee arthroplasty. (C) Postoperative knee joint extension position.

Postoperative treatment

The drainage bottles in the two groups were uniformly treated and removed after 24 h. Antibiotics were routinely applied, and dressing changes were made to observe any redness, swelling, or exudation in the incision. The decision to continue antibiotics was based on the observations. Anticoagulant therapy was administered on the first day after surgery to prevent thrombosis, and routine intravenous analgesia was given to both the control and experimental groups. After extubation, plain radiographs were performed after bedside knee replacement to recheck the position of the prosthesis (Fig. 2B). Routine blood count analysis, 36 biochemical tests, C-reactive protein, erythrocyte sedimentation rate, and other examinations were performed, and the decision to receive blood transfusion was based on the re-examination of hemoglobin values. Two hours after the operation, patients were guided to do ankle pump exercises and, if conditions permitted, static quadriceps exercises. On the first day after the operation, patients were guided to perform straight leg raising exercises and to let their lower limbs droop naturally while sitting in a relaxed position after the drainage tube was removed. Ice salt bags were placed on the knee joint in both the experimental and control groups to improve the flexion and contracture of the knee joint, and the knee joint was stretched by using its gravity (Fig. 2C). On the second day, patients were instructed to stand and walk around the bed. Patients were also taught to do maximum knee joint flexion and extension training at least once a day, and to aim for a 90° range of motion of the knee joint before discharge. If the patient recovered well after one week and had no signs of infection, they were discharged from the hospital. The incision stitches were removed two weeks after the operation. Both groups of patients were advised to keep exercising after leaving the hospital and to continue taking Xarelto until the stitches were removed for reexamination. Patients were informed that if they experienced any discomfort, our department would follow up.

Discussion

Botulinum toxin type A is synthesized by the rod-shaped Clostridium botulinum and is a presynaptic neurotoxin. Botulinum toxin type A cleaves Synaptosome-associated protein of 25 kDa (SNAP-25) to form a 2.5 kDa protein. The mechanism of action of BoNT/A is to prevent the release of acetylcholine from presynaptic nerve terminals by cleavage of SNAP-25 (6). BoNT/A can not only inhibit the release of acetylcholine, but also inhibit the release of noxious neurotransmitters, such as substance P (SP) and excitatory neurotransmitters like glutamate (7). The toxin also blocks autonomic nervous system conduction through sensory fibers and reduces the production of most nociceptive factors acting on receptors (8). The mechanism of action of BoNT/A shows that it has an analgesic effect and relieves excessive muscle contraction. When a motoneuron at the axon terminal is stimulated to generate an action potential depolarization, acetylcholine is released from the cytoplasm into the synaptic cleft. The molecular mode of action of botulinum toxin is achieved through a transport protein chain, the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex. When BoNT/A reaches cholinergic nerve terminals, the toxin heavy chain can specifically bind to glycoproteins, and this specific docking is the result of BoNT/A's high selectivity for cholinergic synapses. After internalization, the light chain of botulinum neurotoxin binds highly specifically to the SNARE protein complex 5. The SNARE protein complex binds to the light chain and prevents acetylcholine vesicles from docking on the inner surface of the cell membrane, resulting in a blockage of vesicle fusion. Target proteins differ between different botulinum toxin serotypes. Botulinum toxin affects the spinal cord pull reflex by blocking intrafusal muscle fibers while sequentially reducing Ia/II signal afferents, reducing muscle tone without affecting muscle strength (reflex inhibition). The mechanism of BoNT/A (9) not only paralyzes the target muscle to play an anti-muscle tension effect, but also blocks the transmission of autonomic nerve fibers in smooth muscle and exocrine glands. The mechanism of action of BoNT/A lays the foundation for the pleiotropy of clinical application.

In 1989, the US Food and Drug Administration (FDA) included BoNT/A in the drug list for the first time, officially opening the clinical application of BoNT/A. Studies have shown that injection of BoNT/A can effectively treat eyelid and facial spasm, correct wrinkles, hyperhidrosis, and tremor (10). Klein first proposed that BONT/A is effective in alleviating human neuropathic pain associated with multiple sclerosis, neuralgia, and peripheral neuropathy. Currently, BoNT/A has been successfully used to treat various types of headaches, migraine, arthritic pain, cerebral palsy with severe acute sialadenitis, and has recently been successfully used in the treatment of small fiber neuropathy, trigeminal neuralgia, and intractable arthralgia. Additionally, the clinical application of BoNT/A has also been extended to the fields of urology and gastroenterology (11).

Advanced knee osteoarthritis is a serious disability and deformity disease that has caused long-term troubles for elderly patients. Although most KOA patients can be treated with TKA, postoperative pain after TKA still plagues joint orthopedists, anesthesiologists, patients, and family members. Currently, there are various methods for TKA analgesia, such as preemptive analgesia, peripheral nerve block, periarticular injection, and multimodal analgesia. However, there is no clinical gold standard for post-TKA analgesia, and further research is

needed to explore this issue. In recent years, research on the application of BoNT/A in knee joints has attracted much attention. Botulinum toxin type A, as the most stable neurotoxin, has analgesic and muscle spasm-relieving effects. Manuel et al. found that the analgesic activity of botulinum toxin type A may be related to the interference with P2X7/CAT/FKN activation of microglia and the inhibition of microglia production of TNF-α (12). Another study has shown that botulinum toxin type A can potentially be used as a treatment for analgesia after total knee arthroplasty in patients with refractory knee flexion contracture (13).

Conflict of interest

The authors declare that they have no competing interest.

Funding

None.

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***Guangda Wang**
Department of Joint Surgery
The Affiliated Yantai Yuhuangding Hospital of Qingdao University
20 Yuhuangding East Road
Yantai
Shandong Province 264000
China
E-mail: gjwk83666@sina.com