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CLINICAL RESEARCH

Is Botulinum Toxin Type A a Valuable Adjunct During Femoral Lengthening? A Randomized Trial

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Abstract

Background Reduced joint ROM and distraction-induced pain are common complaints of patients who have undergone gradual femoral lengthening. Attempts to reduce the effects of lengthening on joint motion have included the use of botulinum toxin to reduce the muscle forces that restrict motion. The benefits of this approach during femoral lengthening, however, have not been conclusively established.

Questions/purposes We wished to evaluate the effects of botulinum toxin type A (BtX-A) injection in the anterior thigh muscles during femoral distraction osteogenesis on adjacent joint ROM and distraction-induced pain. We asked: (1) Does injection of BtX-A in the quadriceps muscles lead to improved knee and hip motion during femoral lengthening? (2) Does injection of BtX-A reduce pain during femoral lengthening?

Methods A single-center, double-blind, randomized placebo-controlled trial was conducted. Forty-four patients (88 femurs) undergoing bilateral femoral lengthening for familial short stature were included in the study. BtX-A (200 IU) was injected intraoperatively in the quadriceps muscles of one thigh. An equal volume of sterile normal saline was injected in the other thigh as a control. Selection of the limb receiving the toxin was randomized. Clinical evaluation included a VAS score for pain measurement, ROM evaluation of the hips and knees, and measurement of thigh circumference. Side-to-side differences were analyzed throughout the entire consolidation phase. No patients were lost to followup, leaving 44 patients (88 femurs). The mean followup was 26 months (range, 14–40 months). The distraction rate and final length of gain were similar between treated and control limbs. A priori power analysis suggested that 44 legs were required in each group to achieve statistical significance of 0.05 with 90% power to detect a 50% difference in treatment effect between treatment and control groups.

Results There were no differences in hip ROM, knee ROM, or maximal thigh circumference between the two lower extremities at any time during the study period. VAS scores were no different between the patients who received BtX-A and those who received saline.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that the informed consent for participation in the study was obtained.
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Conclusions Local injection of 200 IU BtX-A in the quadriceps muscles does not appear to reduce distraction-induced pain nor enhance ROM in the hip or knee during femoral lengthening. Additional studies are needed to evaluate the effect of larger doses or different injection methods. Based on our findings, we do not recommend routine use of botulinum injections during limb lengthening and believe any further use of this drug should only be in the context of a controlled trial.

Level of Evidence Level II, therapeutic study.

Table 1. Demographic data of patients undergoing bilateral femoral lengthening

Variables	Value
Number of patients	44
Number of femoral segments	88
Male:female (number of femurs)	70:18
Age at surgery (years)*	26 ± 8
BMI (kg/m^2)*	21 ± 6
Followup (months)*	26 ± 8

* Values expressed as mean ± SD

Introduction

The success of distraction osteogenesis, or limb lengthening, depends on avoiding complications that may arise because of the treatment. Distraction-induced tension can lead to stiffness of muscles and tendons, resulting in joint contracture and pain [5, 21]. These contractures are thought to result from inadequate adaptation of muscle and soft tissue and a strength imbalance between agonist and antagonist muscles [6, 18]. Stiff knees after femoral lengthening are common and may result from muscle contracture or adhesions [12, 14, 19]. Knee contracture may improve with physiotherapy, but in certain patients, it persists despite intensive physiotherapy. Thus, soft tissue release may be necessary to overcome this complication.

One such option for overcoming soft tissue complications is botulinum toxin type A (BtX-A). BtX-A is known to have analgesic and paralytic actions by blocking

Table 2. Comparison of results between the BtX-A and placebo groups

Variable	BtX-A group*	Placebo group*	Mean difference	95% CI	p value
Hip flexion contracture (°)					
4 weeks	3.8 ± 2.7	5.2 ± 4.7	−1.3	−3 to 0.3	0.10
8 weeks	6.0 ± 4.1	7.6 ± 5.2	−1.6	−3.6 to 0.4	0.11
12 weeks	3.9 ± 5.2	4.6 ± 5.3	−0.7	−2.9 to 1.5	0.54
24 weeks	1.0 ± 2.6	1.1 ± 2.5	−0.1	−1.2 to 1	0.87
48 weeks	0.1 ± 0.7	0.1 ± 0.4	0.2	−0.2 to 0.3	0.86
Knee extension contracture (°)					
4 weeks	0.3 ± 0.7	1.4 ± 3.8	−1.1	−2.3 to 0	0.06
8 weeks	0.6 ± 0.9	1.1 ± 1.6	−0.5	−1.0 to 0.1	0.11
12 weeks	1.0 ± 2.1	1.6 ± 2.4	−0.5	−1.5 to 0.4	0.29
24 weeks	0.1 ± 0.4	0.2 ± 0.6	0.1	−0.3 to 0.2	0.54
48 weeks	0.1 ± 0.4	0.2 ± 0.6	0.1	−0.3 to 0.2	0.54
Maximum thigh circumference (mm)					
4 weeks	38.6 ± 2.8	38.4 ± 2.8	0.3	−0.9 to 1.4	0.68
8 weeks	36.9 ± 1.9	36.7 ± 1.9	0.2	−0.6 to 1	0.61
12 weeks	40.1 ± 1.9	40.2 ± 2.2	-0.1	−0.9 to 0.8	0.83
24 weeks	44.2 ± 4.2	44.0 ± 3.6	0.2	−1.5 to 1.8	0.85
48 weeks	41.5 ± 3.8	40.6 ± 3.6	0.9	−0.7 to 2.4	0.27
Pain VAS (points)					
4 weeks	3.0 ± 2.2	4.0 ± 3.0	-1	−2 to 0.2	0.09
8 weeks	1.6 ± 1.9	1.8 ± 2.2	-0.2	−1.1 to 0.6	0.60
12 weeks	1.3 ± 1.6	1.5 ± 1.6	-0.1	−0.8 to 0.6	0.70
24 weeks	0.6 ± 1.9	0.1 ± 0.9	0.5	−0.2 to 1.1	0.16
48 weeks	0.1 ± 0.8	0.6 ± 1.9	-0.5	−1.1 to 0.1	0.14

* Values are expressed as mean ± SD; BtX-A = botulinum toxin type A

acetylcholine release at the neuromuscular junction [7, 10]. Local injection of BtX-A is commonly used to treat muscle spasticity and contracture in patients with cerebral palsy and brain injury [2, 13, 22, 24]. Numerous authors have described the use of BtX-A during distraction osteogenesis in selected cases [9, 10, 17, 20]. One animal study suggested that the use of BtX-A in distraction osteogenesis decreased the amount of ankle equinus contracture [20]. In some human studies, BtX-A injections appear to be effective for reducing pain and improving ROM during lower limb lengthening [9, 10]. By contrast, Lee et al. [17] showed that local injection of BtX-A did not decrease calf pain or improve ROM during tibial lengthening in adults. We question whether the injection of BtX-A is effective on the same parameters during femoral lengthening. To the best of our knowledge, there have been no studies evaluating the efficacy of BtX-A on ROM or pain reduction in only patients who had femoral lengthening.

We therefore investigated the effect of BtX-A injection in the quadriceps muscle in femoral lengthening osteotomies in the setting of a properly controlled, randomized, double-blind trial. We hypothesized that botulinum injection may increase ROM of the hip and knee and decrease distraction-induced pain by reducing stiffness in the quadriceps muscle. We asked: (1) Does injection of BtX-A in the quadriceps muscles lead to improved knee and hip motion during the lengthening? (2) Does injection of BtX-A reduce pain during femoral lengthening?

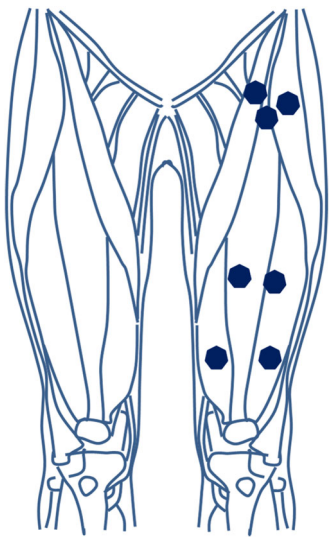

Fig. 1 BtX-A was injected at seven different spots on the anterior thigh. Proximally, the injections were targeted toward the sartorius, rectus femoris, and tensor fascia lata muscles. Distally, the injections were targeted toward the rectus femoris and vastus muscle groups. BtX-A = botulinum toxin type A

Patients and Methods

A placebo-controlled, double-blind, prospective, randomized trial was conducted on 44 patients who underwent bilateral femoral lengthening (88 segments) for familial short statue using intramedullary limb lengthening nails between January 2011 and June 2014. This study was approved by the institutional review board of our institution (BD2011-025D).

Between January 2011 and June 2014, we performed 150 femoral lengthenings in 75 patients using intramedullary limb lengthening nails. Among them, 44 patients consented to participate in the study. No patients were excluded owing to insufficient radiographic and clinical evaluations or were lost to followup. The mean preoperative age of the patients was 26 years. The minimum followup was 14 months (mean, 26 months; range, 14-40 months) (Table 1).

All patients were treated by the same surgeon (DHL). The inclusion criteria for patients in the study were: (1) skeletally mature; (2) no history of medical illness, fracture, soft tissue compromise, bony deformities, or infections of the lower extremity; (3) bilateral limb length discrepancy requiring similar amounts of lengthening of the femurs; and (4) use of the same lengthening method: either the Intramedullary Skeletal Kinetic distractors (ISKD®; Orthofix Inc, Lewisville, TX, USA) or the PRECICE® system (NuVasive Inc [formerly Ellipse Technologies Inc], Aliso Viejo, CA, USA). Patients provided informed consent after receiving an explanation of the rationale and risks of the study; patients had to agree to receive the botulinum injections in one thigh and saline in the other.

All operations were performed by the senior author (DHL). The surgeon switched the type of intramedullary limb lengthening nail during the study period. The ISKD® was used from January 2011 to January 2012, and PRECICE® nails were used between February 2012 and June 2014. The same surgical technique was used for both limbs. In other words, each patient was treated with either the ISKD® (13 patients) or PRECICE® nails (31 patients), but no patient received a different procedure on each limb. The surgical procedures were performed with the patients receiving general anesthesia and positioned on fracture tables. First, the lesser trochanter was imaged with the patella forward. Two parallel 5-mm Schanz pins were inserted proximal and distal to the osteotomy site as reference points for rotational alignment. Multiple drilling was done in the osteotomy site through a 1-cm incision. The entry point for the nail was either at the piriformis fossa or at the tip of the greater trochanter. The location of the entry point was determined preoperatively. The medullary canal was overreamed by a minimum of 1.5 to 2

mm wider than the nail diameter used, and then careful percutaneous osteotomy was conducted to complete the transverse osteotomy. Subsequently, the nail was inserted and the interlocking screws were fixed. The BtX-A injection was administered intraoperatively at the end of all surgical procedures. Briefly, 200 IU BtX-A (BOTOX® Purified Neurotoxin Complex; Allergan Inc, Irvine, CA, USA) was mixed with 20 mL sterile, normal saline. The same amount of sterile, normal saline was prepared for the control limb. Selection of the limb receiving the toxin was randomized and each patient served as his or her control. The injection was distributed evenly over seven different spots on the anterior thigh in the quadriceps muscle (Fig. 1). Injection was performed manually with no assistance from instrumentation such as electromyography or ultrasound.

The surgeon (DHL) did not know which syringe contained BtX-A. Patients also were blinded and did not know which limb was injected with BtX-A. Postoperatively, all patients were instructed how to lengthen their limbs and modify their daily activities. Each patient had a 1-week latent period and then began the distraction period. The target distraction rate was set at 1.0 to 1.2 mm per day. The mean distraction rate was 1.28 ± 0.14 mm per day in the BtX-A group and 1.27 ± 0.12 mm per day in the placebo group. There was no significant difference between the two groups (mean difference, 0.01; 95% CI, −0.05 to 0.06; p = 0.87). The mean final length gain was 54 ± 6 mm in the BtX-A group and 55 ± 6 mm in the placebo group, a difference that was not statistically significant (mean difference, −0.16; 95% CI, −2.67 to 2.36; p = 0.96). Because all patients underwent bilateral limb lengthening, they were allowed to move using a wheelchair only until there was radiographic evidence of two cortical consolidations. Full weightbearing was permitted thereafter. Patients were monitored once per week during the distraction phase and every month thereafter until the end of the consolidation phase. Pain was managed using a previously published protocol [17]. A patient-controlled analgesic (430 μg mixed sufentanil citrate with 100 mL normal saline; BCworld Pharm Co Ltd, Yoeju, Korea) was placed at the end of the surgery and maintained until postoperative Day 2. Afterward, Ultracet® (Janssen Korea Ltd, Seoul, Korea) was administered twice per day. Intravenous Zipan® (Ilsung Pharmaceuticals Co Ltd, Seoul, Korea) was injected as needed, up to three times a day. For severe pain, Targin® (Mundipharma Korea Ltd, Seoul, Korea) was given as a rescue medication.

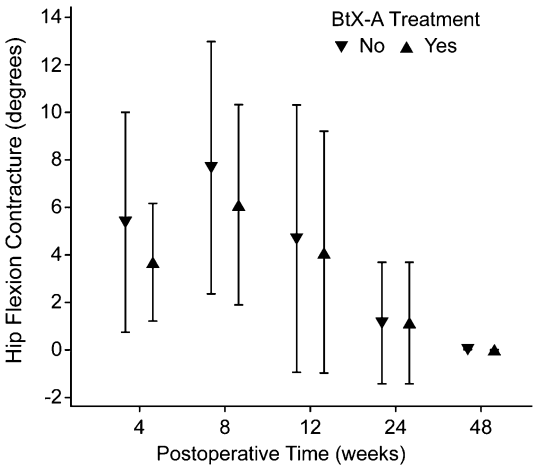

Fig. 2 Postoperative hip flexion contracture in the BtX-A and placebo groups showed no significant difference between the two groups at any measured time. ▼ and ▲ = mean value; bars = SD; BtX-A = botulinum toxin type A

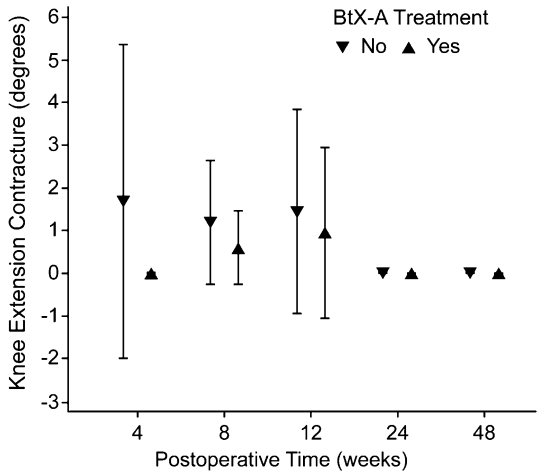

Fig. 3 Postoperative knee extension contracture in the BtX-A and placebo groups showed there was no significant difference between the two groups at any measured time. ▼ and ▲ = mean value; bars = SD; BtX-A = botulinum toxin type A

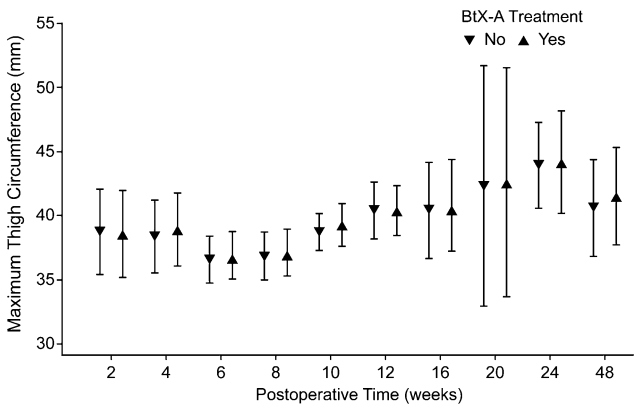

Fig. 4 The mean postoperative VAS scores in the BtX-A and placebo groups showed no significant side-to-side differences between the two groups at any measured time. ▼ and ▲ = mean value; bars = SD; BtX-A = botulinum toxin type A

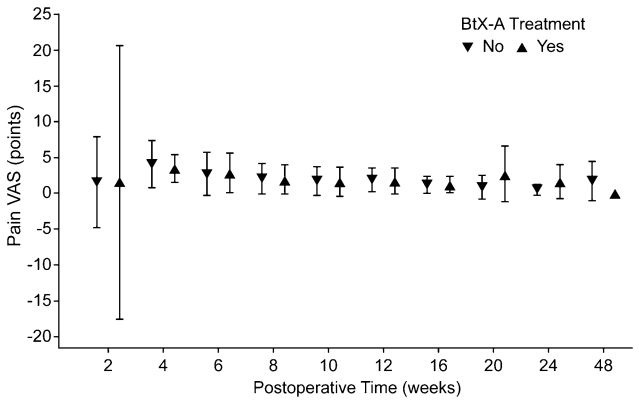

Fig. 5 The mean maximal thigh circumferences in the BtX-A and placebo groups showed no significant side-to-side differences between the two groups at any measured time. ▼ and ▲ = mean value; bars = SD; BtX-A = botulinum toxin type A

Clinical assessments were recorded on a standard data collection sheet by two orthopaedic residents (DWK, JJH) who were blinded to the patients' medical records. Evaluations included ROM of the hips and knees using a handheld goniometer and pain in thigh muscle areas based on a VAS for pain (0–10 points). Using a pain questionnaire, each patient was asked to record pain VAS at each leg and to describe the location of the pain (anterior or posterior thigh). Because the BtX-A injection may cause muscle atrophy or a decrease in muscle mass [8, 23], the maximal thigh circumference (in mm) was measured manually with a tape measure to investigate the changes of muscle mass. Then, the side-to-side differences were analyzed at each followup. All patients were asked whether they experienced any injection-related adverse events, including flu-like syndrome, dysphagia, dry mouth, headache, or nausea.

Statistical Analysis

At the beginning of the study, we performed an a priori power analysis for the three clinical variables we intended to measure: hip and knee ROM, pain in the anterior thigh muscle area, and maximal thigh circumference. This analysis showed that a minimum sample size of 44 legs was required to achieve statistical significance of 0.05 with 90% power at an effect size of 0.5 for VAS score (that is, 90% power to detect a 50% difference between the treatment and placebo groups). Thus, we had 44 legs (22 patients) in each group, which is equal to the minimum sample size. All three continuous measurements (hip and knee ROM, anterior thigh pain, and maximal thigh circumference) were tested for normality using the Shapiro-Wilk test and did not violate the normal-distribution assumption. Side-to-side differences (BtX-A group versus placebo group) were measured at each followup and analyzed using the paired t-test. A p value less than 0.05 was considered statistically significant. The statistical software R (Version 2.12; The R Project for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

Results

Results for the BtX-A group and the placebo group are summarized (Table 2). Hip ROM, especially flexion contracture, showed no differences between the treatment and control groups at any time (Fig. 2). Likewise, knee ROM, especially extension contracture, revealed no differences at any measured time (Fig. 3). Thus, with this dose and manner of administration, BtX-A injection did not influence ROM after this procedure in our patients. Additionally, the mean maximal thigh circumference was not different between groups at any time measured (Fig. 4). We observed no BtX-A injection-related adverse events.

This analysis showed that BtX-A injection produced no side-to-side differences in distraction-induced pain levels at any time measured (Fig. 5).

Discussion

Decreased ROM of the hip and knee occurs frequently during femoral lengthening. More specifically, extension of the hip and flexion of the knee decrease because of tightness in the quadriceps [1, 3, 25]. To prevent this complication, BtX-A injections seem to be an appealing option; however, prior studies have disagreed regarding whether BtX-A is effective [9, 10, 17]. Previously, Lee et al. [17] reported that BtX-A injection in the calf muscle during tibial lengthening was not effective. Because muscle contractures after femoral lengthening were not uncommon and muscle structure of the femur is not the same as that of the tibia, we questioned whether the effect of BtX-A injection during femoral lengthening is similar to that with tibia lengthening. Similarly, in this study, we show that BtX-A injection in the thigh muscle did not reduce pain or increase ROM during femoral lengthening.

Our study has some limitations. First, we did not test a range of BtX-A doses. It is possible that our selected dose was not effective. Hamdy et al. [9–11] used a weight-based dose (10 IU/kg, up to maximal 400 IU) and concluded the injection of BtX-A during lengthening osteotomy was effective in pediatric patients. We used 200 IU as a standard dose on one muscle compartment for all patients because the injections were limited to the quadriceps muscles. However, the actual mean dose of BtX-A injected

was 3.6 IU/kg (range, 2.9-5.0 IU/kg) which is a smaller dose than those used in previous studies [9–11]. Therefore, a different dose, dilution, or schedule, or the use of repeated injections, may provide improvement. Second, two types of internal devices were used to achieve lengthening in this patient cohort. However, the use of these devices was distributed evenly between the groups, and therefore we think this limitation does not jeopardize our conclusions. Third, the BtX-A injection was done only in the quadriceps muscles. We did not consider the hamstring muscle as an injection site because the study focused on the problem of knee flexion resulting from tightness in the quadriceps [1, 25]. To evaluate knee flexion contracture, BtX-A injections in the hamstring muscle will be needed. Fourth, injections were performed manually. Ultrasound-guided methods might allow for more accurate injections. Fifth, VAS scores are based on patients' subjective, personal assessments, and it is possible they could not accurately identify where the pain originated. As a result, it is difficult to ensure that the VAS scores provided by patients represent the actual pain experienced during their followups.

We found that with the dose and schedule of administration we used, the botulinum injections did not lead to improved ROM compared with a placebo saline injection. A multicenter study in children undergoing distraction osteogenesis showed that BtX-A injections reduce pain, increase quality of life, and improve functional mobility scores; a weight-based dose (10 IU/kg), up to a maximum of 400 IU was used [9, 10]. We used a standard dose (200 IU) on anterior thigh muscles, but did not observe differences between treatment and placebo groups. One possible explanation for these contrasting data is the dose of BtX-A used. However, we think that the differences in dosage between a multicenter study [11] and our study are minimal because the former used a maximum of 200 IU in any single muscle compartment. More likely, this discordance is the result of differences of study patients between previous studies and our study, because children have relatively looser soft tissues than adults. Moreover, several differences existed between previous studies [9, 10] and our study with respect to surgical site location, pain management protocols, and multiple etiologies leading to the limb length discrepancies being treated. Intramedullary lengthening devices were developed to avoid the use of external pins or wires, which can result in muscle adhesion or fibrosis. Distraction osteogenesis using these devices maintains good adjacent joint motion compared with lengthening using external fixators. However, several studies have reported an observed loss of knee ROM despite lengthening using an internal lengthening device [4, 15, 16]. Given other applications for BtX-A, we rationalized that BtX-A injections were an appropriate treatment to investigate in our study, because muscle structure is well preserved during the use of internal lengthening devices.

Lengthening-induced pain was not alleviated with the injection of BtX-A in our patients, and this finding was not in accordance with those of previous studies [9, 10]. This could be attributable to the doses or sites of BtX-A injection. Although we injected BtX-A in only the quadriceps muscle, Hamdy et al. [11] injected the quadriceps and hamstring muscles in patients undergoing femoral lengthening.

We found that the injection of BtX-A (200 IU) in the quadriceps muscles during femoral lengthening did not effectively enhance ROM of the adjacent joints or decrease distraction-induced pain. However, additional studies that evaluate different BtX-A doses or different injection methods and schedules may show a better use for this technique in managing patient recovery after femoral lengthening procedures. Based on our findings, we do not recommend routine use of botulinum injections during limb lengthening and believe any additional use of this drug should be in the context of a controlled trial.

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