

RESEARCH ARTICLE

# Comparison of the effects of botulinum toxin type A hamstring muscle injection combined with periarticular injection and simple periarticular injection on early pain and functional recovery after total knee arthroplasty

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## Abstract

**Objective:** This study was designed to compare the effects of hamstring muscle injection of botulinum toxin type A (BoNT/A) combined with periarticular injection to those of simple periarticular injection alone, in terms of early pain reduction and functional recovery following total knee arthroplasty (TKA).

**Methods:** This study included 40 patients who underwent elective unilateral TKA at our hospital from February 2021 to December 2021. The patients were randomly assigned to either the experimental group (BoNT/A injection into the hamstring muscle + periarticular injection,  $n = 20$  cases) or the control group (0.9% normal saline injection into the hamstring muscle + periarticular injection,  $n = 20$  cases). The preoperative and postoperative 3-day HSS scores were compared between the two groups. Postoperative visual analog scale (VAS) pain scores were observed and compared between the two groups. The Lovett grading method was used to evaluate the postoperative muscle strength of both groups. Additionally, postoperative knee joint pain scores, maximum active flexion angle, and any postoperative adverse reactions were observed and compared between the two groups.

**Results:** The experimental group showed significantly lower VAS pain scores than the control group at 24 h, 48 h, and 72 h after the operation, with a statistically significant difference ( $P < 0.05$ ). Furthermore, compared to the control group, the patients in the experimental group exhibited larger knee joint active flexion angles at 1 day, 3 days, and 5 days post-operation, also demonstrating a statistically significant difference ( $P < 0.05$ ). These findings hold scientific significance ( $P < 0.05$ ). Additionally, the combined administration of BoNT/A hamstring muscle injection with periarticular injection exhibited a low incidence of adverse reactions during the perioperative period and had no significant effect on quadriceps muscle strength.

**Conclusion:** The combination of BoNT/A hamstring muscle injection with periarticular injection effectively alleviates early postoperative pain following TKA and promotes early functional recovery of the knee joint.

**Keywords:** total knee arthroplasty; botulinum toxin type A; periarticular injections; hamstring injections; analgesia; functional rehabilitation

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**K**nee osteoarthritis (KOA) is a chronic disease that has a high incidence among the elderly (1). The treatment of KOA is divided into conservative methods involving physical therapy and medication, and surgical intervention is considered when conservative

treatments yield poor or ineffective results (2). Although drug therapy remains the primary approach for treating KOA (3), it also has its limitations (4), such as restricted drug administration (intra-articular injection) and the potential for serious adverse reactions. Furthermore, drug

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therapy only provides relief for the clinical symptoms of KOA and does not have the ability to delay the progression of arthritis.

Severe pain after TKA is a source of fear and suffering for the majority of patients. Inadequate pain control following TKA can substantially raise the occurrence of perioperative complications (5) and impact the long-term prognosis of patients. Thus, achieving optimal analgesia after TKA is crucial to decrease the frequency of perioperative complications and adverse reactions. Pain management approaches have advanced over the past decades (6), yet a flawless, ideal pain management strategy remains elusive.

Botulinum toxin type A (BoNT/A) is produced by the rod-shaped bacterium *Clostridium botulinum* and is classified as a presynaptic neurotoxin. The mechanism of action of BoNT/A involves its analgesic effects and its ability to relieve excessive muscle contractions. Studies have demonstrated that the injection of BoNT/A can effectively treat conditions such as eyelid and facial spasms, wrinkles, hyperhidrosis and tremors (7). Klein was the first to propose that BoNT/A is effective in alleviating neuropathic pain associated with multiple sclerosis, neuralgia, and peripheral neuropathy in humans. Currently, BoNT/A has been successfully utilized in the treatment of various types of headaches, migraines, arthritic pain, and severe acute sialadenitis in cerebral palsy patients, and more recently, it has shown promise in the treatment of small fiber neuropathy, trigeminal neuralgia, and intractable arthralgia. Moreover, the clinical application of BoNT/A has also expanded to urology and gastroenterology fields (8).

In recent years, there has been significant research interest in the application of BoNT/A in knee joints. Botulinum toxin type A, known for its stability, possesses analgesic and muscle spasm-relieving properties. Manuel et al. discovered that the analgesic effects of BoNT/A may be associated with its interference in the activation of P2X7/CAT/FKN pathway in microglia, as well as its regulation of FKN to inhibit microglial production of TNF- (9). Studies conducted by Seyler and colleagues have demonstrated the potential of BoNT/A as a treatment option for pain relief following total knee arthroplasty (TKA) in patients with refractory knee flexion contracture (10).

We compared the combination of BoNT/A hamstring muscle injection with periarticular injection to simple peripheral nerve injection in this experiment. We observed the postoperative visual analog scale (VAS) pain scores in both groups, evaluated the quadriceps muscle strength using the Lovett grading method, and recorded the postoperative pain scores for both groups. Additionally, we analyzed the maximum active flexion and extension

range of the posterior knee joint to assess the impact of BoNT/A hamstring muscle injection on analgesia and early functional rehabilitation after TKA.

## Methods and materials

### Participants

A total of 40 patients with primary unilateral KOA who required surgery in the Department of Joint Orthopedics at Yantai Yuhuangding Hospital between February 2021 and December 2021 were selected. The study population consisted of 13 males and 27 females, aged 55–65 years, and they were randomly divided into two groups: the control group and the experimental group, each containing 20 cases. The body mass index (BMI) ranged from 20 to 30 kg/m<sup>2</sup>.

After obtaining review and approval from the Ethics Committee of Yantai Yuhuangding Hospital ([2020] No. 303) and engaging in active communication with the participating patients and their families, informed consent was obtained. The patients and their families agreed to sign the necessary operation and related documents, indicating their understanding and voluntary participation. Detailed information about the study groups was not disclosed to the patients, escorts, or medical staff.

### Drugs and equipment

Botulinum toxin type A (Lanzhou Biotechnology Development Co., Ltd., S10970037, trade name ‘Hengli’ 50 units/bottle, diluted with normal saline to 1 mL), cocktail (recipe: ropivacaine 150 mg + triamcinolone acetate 1 mg + morphine 10 mg, normal saline diluted to 60 mL), American Zimmer artificial surface posterior stabilized prosthesis (Nexgen-LPS high flexion), 400 mL negative pressure drainage bottle, tranexamic acid injection, knee replacement device.

### Surgical procedures

Please refer to our previous article published on this topic (11) for patient inclusion and exclusion criteria as well as detailed surgical procedures.

### Knee HSS score

The preoperative HSS scores were recorded for KOA patients in both groups. The HSS score represents a percentage rating system used for evaluating the knee joint, taking into account factors such as pain, activity, and others to assess KOA patients from seven different aspects. The system is divided into four functional grades: excellent (85–100 points), good (70–84 points), general (60–69 points), and poor ( $\leq 60$  points). Surgical treatment is required for KOA patients if their preoperative HSS score is below 69 points, and the X-ray confirms significant narrowing of the knee joint space. Furthermore, the HSS score serves as the gold standard for assessing outcomes after TKA (12).

### Visual analog scale pain score

The pain degree of patients in both the control group and the experimental group was evaluated using the VAS at 24 h, 48 h, and 72 h after the operation. The scoring standard ranged from 0 to 10 points, where 0 indicated no pain, and the numerical value represented the degree of pain (13). To determine the pain intensity, patients were asked to mark the position on the scale that best reflected their level of pain.

### Lovett muscle strength scale

The quadriceps muscle strength of the patients in the control group and the experimental group was evaluated using the Lovett grading method 1 day, 2 days, and 3 days after the operation.

### Maximum knee flexion

The range of motion of the knee joint after surgery can reflect the effectiveness of TKA and postoperative exercise. The maximum range of motion was measured in both the control group and the experimental group on postoperative days 1, 3, and 5.

## Statistical analysis

The data were analyzed using SPSS 25.0 statistical analysis software to compare the differences. Prior to analyzing the measurement data, the Shapiro-Wilk normality test was conducted on the experimental data. Normally distributed data were presented as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) and analyzed using an independent t-test. Non-normally distributed data were presented as quartiles (p50[p25, p75]) and analyzed using the non-parametric Mann-Whitney U test. Statistical significance was determined at  $P < 0.05$  for all results.

## Results

### Comparison of general conditions of the patients

The factors including age, knee contracture, and preoperative HSS score exhibited a  $P$ -value greater than 0.05 when comparing the control group and the experimental group. The lack of statistical significance suggests that the samples from both groups possessed comparable characteristics (Table 1), excluding any objective factors.

### Postoperative observation indexes

After TKA, there was a statistically significant difference in VAS pain scores (at 24, 48, and 72 h) between the experimental group and the control group ( $P < 0.05$ ) (Table 2). The quadriceps muscle strength analysis of the affected limb showed no statistically significant difference between

the two groups after the operation at 1 day, 2 days, and 3 days (Table 3).

Statistically significant differences were observed in the maximum range of motion of the knee joint between the experimental group and the control group at 1 day, 3 days, and 5 days ( $P < 0.05$ ) (Table 4). Univariate analysis of the HSS scores at 3 days after the operation revealed statistically significant differences between the two groups ( $P < 0.05$ ).

### Postoperative complications and adverse reactions

No serious complications such as incision infection, Venous thromboembolism (VTE), or hypostatic pneumonia occurred in either of the two groups. In the control group, five patients received pethidine hydrochloride injection for postoperative pain relief, while only one person in the experimental group received the same treatment. Nausea and vomiting were experienced by two patients in the experimental group and three patients in the control group. However, these adverse reactions were mild and resolved spontaneously without requiring symptomatic treatment. Bruises were observed at the rear of the knee joint in three patients from the experimental group following the surgery, which could possibly be attributed to the side effects of the tourniquet, and no other significant adverse reactions were observed. The hemoglobin levels in both groups did not meet the criteria for blood transfusion.

## Discussion

The safety and effectiveness of BoNT/A treatment have gained worldwide recognition (14). In a randomized controlled trial, Rezasoltani et al. concluded that intra-articular injection of BoNT/A effectively relieves pain and symptoms in patients with KOA (15). In an early phase 1b study, McAlindon found that BoNT/A effectively reduces nociceptive pain associated with knee OA (16). Studies have demonstrated that BoNT/A can alleviate the increase in muscle tone caused by TeNT (17). Okamoto et al. reported that myogenic contracture in the knee joint, induced by inflammatory mediators, is a contributing factor to KOA-related mobility limitation, and intramuscular injection of BoNT/A significantly delays its progression (18).

Based on the experience of using BoNT/A in the treatment of other pain conditions and the related studies published on intra-articular injection of BoNT/A (19), the most commonly utilized doses are 100 units and 200 units. However, current studies do not support the use of 200 units as the recommended dosage for intra-articular injection. It is worth noting that there was no increase in adverse reactions observed in the high-dose botulinum

Table 1. Comparison of general conditions

	Age	Knee contracture	Preoperative HSS score
Control group	60.20 $\pm$ 2.60	15.25 $\pm$ 2.75	44.65 $\pm$ 3.34
Experimental group	59.40 $\pm$ 2.50	15.15 $\pm$ 2.43	44.50 $\pm$ 3.34
$P$	>0.05	>0.05	>0.05

Table 2. Postoperative pain score in two groups of patients

	24 h post-operation	48 h post-operation	72 h post-operation
Control group	4.75 $\pm$ 1.11	4.05 $\pm$ 0.82	3.40 $\pm$ 0.75
Experimental group	4.15 $\pm$ 0.67	3.40 $\pm$ 0.59	2.85 $\pm$ 0.58
$P$	0.046	0.007	0.014

**Table 3.** The maximum active flexion of the knee joint and the HSS observation index after 3 days in the two groups of patients

	1 d post-operation	3 d post-operation	5 d post-operation	Postoperative HSS
Control group	57.65 ± 3.00	68.20 ± 2.91	77.60 ± 2.66	55.35 ± 2.39
Experimental group	60.10 ± 2.81	70.45 ± 2.23	80.20 ± 2.21	57.70 ± 2.38
<i>P</i>	0.011	0.009	0.002	0.004

**Table 4.** Observation of quadriceps femoris muscle strength in two groups of patients after operation

	1 d post-operation	2 d post-operation	3 d post-operation
Control group	4(4.5)	4(4.5)	5(4.5)
Experimental group	4(4.5)	4(4.5)	5(4.5)
<i>P</i>	>0.05	>0.05	>0.05

toxin group. Nevertheless, it is important to acknowledge that the follow-up period was only 6 months, and potential long-term adverse effects cannot be ruled out. Side effects of BoNT/A typically occur within the first 2 weeks after injection and are usually temporary. These may include localized pain, tenderness, and bruising at the injection site. In some cases, the toxin may spread and cause weakness in adjacent muscles, although allergic reactions are rare. Among the 36 randomized controlled trials conducted, involving a total of 1425 patients who received extensive use of BoNT/A, no serious adverse reactions were reported. Therefore, BoNT/A injection is considered to be safe and well-tolerated (20).

In this study, we employed periarticular injection combined with BoNT/A hamstring muscle injection for postoperative analgesia following knee arthroplasty. The efficacy of analgesia was assessed using the VAS pain score. The results revealed that the pain score in the experimental group was significantly lower than that in the control group ( $P < 0.05$ ). Furthermore, the experimental group required a lower rescue dose of pethidine hydrochloride injection, indicating that the analgesic effect of BoNT/A injection, in conjunction with periarticular injection in the hamstring muscle, was superior during the initial week.

Following TKA, patients commonly experience severe pain when in a straightened position. Therefore, it is recommended that patients initiate straightening exercises for the affected limb 24 h after the surgery. This involves raising the heel pad, applying an ice salt bag to the knee joint, and utilizing gravity to maintain knee joint extension. Compared to patients without knee flexion contracture, those with contracture tend to experience greater early postoperative pain after TKA. Additionally, there are individual differences in subjective pain sensitivity among patients. These factors collectively contribute to the observed decreasing trend in pain scores at 24 h post-surgery in this study.

Muscle strength plays a crucial role in joint stability following TKA, and joint stability exhibits a positive correlation with muscle strength. When comparing quadriceps muscle strength using the Lovett classification method, there was minimal difference between the experimental group and the control group in early postoperative muscle strength, and this difference was not statistically significant ( $P > 0.05$ ). This experiment demonstrates that injecting BoNT/A into the hamstring muscle, in addition to periarticular injection, has no significant impact on muscle strength after TKA. In this experiment, patients exhibited weak muscle strength on the first and second days after the operation. It is speculated that the primary reason for this could be the limited activity caused by postoperative pain stimulation, leading to the clinical observation of weakened muscle strength. It is also possible that the application of high pressure from the tourniquet during the operation resulted in weak postoperative thigh muscle strength. The current research sample is small, and the observation time is short. Further extensive follow-up is needed to assess the long-term effects of BoNT/A on quadriceps muscle.

There are still some limitations in this experiment. Each patient exhibits varying degrees of pain sensitivity, resulting in differences in the selection of VAS pain scores when responding to the same intensity of stimulation. While it would be ideal to choose the same patient for bilateral TKA as the research subject, comparing the postoperative pain levels in both knees could significantly reduce inter-individual variability. However, the majority of clinical patients are elderly and may not be suitable candidates for bilateral TKA due to their physical condition. This has affected factors such as inter-rater error and the reliability of muscle strength comparisons between the two groups. In the experiment, there was a lack of precision in positioning the hamstring muscle, with a primary focus on the semimembranosus. Additionally, the small sample size and short hospitalization time of this study, coupled with the impact of the epidemic, resulted in a significant number of patients being lost to follow-up at 1 month and 3 months. Therefore, a comprehensive understanding and documentation of the long-term follow-up and clinical effectiveness of postoperative outcomes are still needed.

## Conclusions

Combining BoNT/A injection into the hamstring muscles with periarticular injection has been shown to effectively alleviate



early pain following TKA and enhance early functional recovery of the knee joint. However, this treatment does not significantly impact quadriceps muscle strength, and the occurrence rate of adverse reactions is low. This approach establishes a basis for early postoperative exercise and, simultaneously, improves knee joint function more rapidly and effectively. It represents a novel avenue for early analgesic management in TKA and sets a new direction for future research.

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