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Original Article

Continuous Femoral Nerve Block versus Patient-Controlled Intravenous Analgesia for Patients Undergoing Unilateral Total Knee Arthroplasty: A Cost-Effectiveness Analysis and Cost-Utility Analysis

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ABSTRACT

Background: In order to relieve pain following total knee arthroplasty (TKA), patient-controlled intravenous analgesia (PCIA) and continuous femoral nerve block (CFNB) are commonly used for postoperative analgesia. Nowadays, anesthesiologists are more and more interested in reducing patients' financial burden while providing effective analgesia. Therefore, this study investigated the cost-effectiveness and cost-utility of CFNB versus PCIA for patients undergoing unilateral TKA.

Methods: Patients were randomly divided into CFNB group and PCIA group. Ultrasound-guided femoral nerve block was performed for CFNB group, and PCIA was used in the other group. The effects of analgesia during hospital stay, pain intensity and knee function at 6 months after discharge were evaluated. The cost of analgesia, direct medical cost, indirect cost, total cost, cost-effectiveness ratio, cost-utility ratio, and incremental cost-effectiveness ratio were calculated.

Results: Compared with the PCIA group, the rate of incomplete analgesia, mean frequency of rescue treatment, mean dose of drugs used for rescue treatment, and mean length of postoperative hospital stay decreased in the CFNB group (PCIA: N=123, CFNB: N=127). In the CFNB group, pain score decreased, knee function improved (PCIA: N=123, CFNB: N=127), and the quality of life score increased at 6 months after surgery (PCIA: N=102, CFNB: N=109). Analysis of economic outcomes showed that the mean cost of analgesia in the CFNB group was higher than that of the PCIA group (PCIA: N=123, CFNB: N=127), but the mean direct cost and total cost in the CFNB group were lower at 6 months after surgery (PCIA: N=102, CFNB: N=109).

Conclusions: Compared with PCIA, CFNB reduced acute and chronic pain after TKA, improved short-term and long-term function of knee, and improved patients' quality of life with better cost-effectiveness and cost-utility.

Total knee arthroplasty (TKA) can effectively treat end-stage osteoarthritis by relieving pain and improving knee joint function (1). However, moderate-to-severe pain following TKA not only makes patients stressful, but also impairs early exercise of the knee joint and increases the risk of postoperative complications (2). With the evolution of anesthesia techniques, clinicians try to minimize pain and reduce the cost of anesthesia and analgesia. Therefore, anesthesiologists are more and more interested in reducing patients' financial burden while providing effective analgesia (3). In order to relieve pain following TKA, two methods are commonly used for postoperative analgesia: patient-controlled intravenous analgesia (PCIA) and continuous femoral nerve block (CFNB). Many studies found CFNB was superior to PCIA in controlling acute pain at 1-3 days postoperatively (4, 5). However, most studies have evaluated short-term outcomes without assessing the health economic consequences associated with these treatments. And few studies have been conducted to evaluate the chronic pain and medium-term knee function. Thus, we studied cost effectiveness and medium-term effects of the two analgesic methods for patients undergoing TKA.

In the present study, we examined the effects of CFNB and PCIA on short-term and long-term pain, knee joint function and quality of life, and performed the cost-effectiveness analysis and cost-utility analysis, so as to provide more comprehensive evidences of optimal analgesia for patients undergoing TKA.

MATERIALS AND METHODS

Participants

The randomized controlled study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University in advance and registered in Chinese Clinical Trail Registry (No. ChiCTR-ONRC-14004247). All subjects were provided with written, informed consents. The protocol was designed and conducted in accordance with Consolidated Standards of Reporting Trails Statement (6). Inclusion criteria: patients between 18 and 75 years old who underwent selective unilateral TKA. Exclusion criteria included the following: 1) patients with American Society of Anesthesiologists (ASA) grade IV or V; 2) patients whose body mass index (BMI) was >35; 3) patients who had neuropsychological dysfunction; 4) patients who had bilateral knee replacement or knee surgery not interfering with articular joint cavity (such as wound debridement and suture) or the second knee revision surgery; 5) patients who had uncontrolled systemic infection; 6) patients who had severe coagulation disorders or active stomach ulcers or who were administered anticoagulants; 7) patients who had local infection at the site of the femoral nerve block or known allergic reactions to the local anesthetic drugs and other drugs used during surgery; and 8) patients who had intraoperative respiratory arrest or cardiac arrest.

Statistics Analysis System software (SAS) proc plan procedure was used to generate a random number. The number of every patient was concealed in opaque envelopes. The envelope was not opened until the patient was enrolled in this study.

Types of Anesthesia

General anesthesia was performed in participants. After rapid intravenous induction and subsequent intubation, controlled ventilation was provided. Heart rate, respiratory rate, temperature, pulse oximetry, and invasive arterial pressure were monitored. Anesthesia was maintained by sevoflurane (1% to 3%) with continuous intravenous infusion of propofol (25-75 μg/kg/min) and remifentanil (7-8 μg/kg/h) with microperfusion pump. Fluid therapy was administered at 5-10 ml/kg/h. Vasodilators, vasoconstrictors, and diuretics were used when necessary to maintain hemodynamic stability. A group of senior anesthesiologists performed anesthesia and analgesia for patients. Similarly, one team of senior surgeons performed the operation for patients.

Types of Postoperative Analgesia

In the CFNB group, anesthesiologists performed the femoral nerve block on the operated leg before induction of anesthesia. All patients extended their legs for block placement while lying on the operating room table. After sterile preparation, we used ultrasound to identify the puncture site, 1-2 cm lateral to the femoral artery and 2 cm distal to the inguinal ligament. After topical anesthesia with 2% lidocaine, we connected an insulated needle (20 G 45 mm, short bevel, 30°) (Contiplex Braun, Melsungen, Germany) to the nerve stimulator with the stimulating intensity of 1 mA at a rate of 2 Hz (Innervator, Fisher & Paykel, New Zealand). The needle was advanced at 30°-45° angle to the skin, until quadriceps femoral muscle twitches were elicited. When muscle contraction still occurred with 0.3 mA, the needle position was felt to be correct. Then, the patients were given an initial anesthetic dose with 10 ml of 2% lidocaine and 10 ml of 1% ropivacaine. The catheter remained in place for 10-15 cm. To confirm the correct position of the catheter, the cutaneous sensation in the area of the femoral nerve was assessed using a cold test (7). 30 minutes before the end of the operation, the catheter was connected to the femoral nerve catheter pump. Parameters of the pump were as follows: The loading dose was 5 ml of 0.15% ropivacaine, the background infusion rate was 5 ml/h, the dose of analgesic bolus was 5 ml, and the lockout time was 30 minutes.

In the PCIA group, intravenous access was established for PCIA 30 minutes before the end of surgery and then was connected to the patient-controlled analgesia pump. The regimen of the PCIA analgesia pump was as follows: 800 mg tramadol, 100 mg flurbiprofen axetil, and 5 mg dexamethasone and 0.9% saline into a total of 80 ml solution. The parameters of the analgesia pump were as follows: The loading dose was 2 ml, the background infusion rate was 1 ml/h, the dose of analgesic bolus was 2 ml, and the time of secure lockout was 15 minutes. All patients were given 4 mg ondansetron intravenously to prevent postoperative nausea and vomiting. In both groups, the analgesia pump was removed at 72 hours post-operatively.

Rescue Analgesia Protocol

Pain intensity was evaluated during the use of PCA and non-PCA periods. Rescue analgesia was used for patients whose numerical rating score (NRS) ≥4 (a scale contained number 1 to 10, 0 represents no pain and 10 represents worst possible pain). The first step was to adjust the parameters of the analgesia pump as follows: In the CFNB group, we increased the infusion rate by 1 ml/h each time (the maximum rate was 10 ml/h) or (and) increased the dose of analgesic bolus by 1 ml each time additionally after pain evaluation (the maximum dose was 10 ml); in the PCIA group, we increased the fusion rate by 0.1 ml/h each time (the maximum rate was 1.5 ml/h) or (and) increased the dose of analgesic bolus by 1 ml each time additionally after pain evaluation (the maximum dose was 5 ml, and the maximum daily dose of tramadol was 400 mg). Pain intensity was repeated 30 minutes later. If the NRS was still ≥4, ultrasound examination was performed in the CFNB group, and the location of the catheter was identified. If the catheter fell out or was displaced, the catheter would be extracted and counted as one with analgesic adverse events. Patients in the CFNB group were injected intravenously with non-opioid rescue analgesics: Parecoxib sodium 40 mg (80mg daily maximally was used) and (or) tramadol 1.5 mg/kg (400 mg daily maximally was used). Finally, the opioid rescue medication (Pethidine, intramuscular, 1 mg/kg) was used if the non-opioid medications were considered ineffective (NRS≥4) at 30 minutes after intravenous injection. Patients in the PCIA group were injected intramuscularly with Pethidine 1 mg/kg.

Outcomes Measurement

Baseline Characteristics

Baseline characteristics included pre-operative items: age, height, weight, gender, ASA grade, NRS, knee flexion, Western Ontario and McMaster Universities (WOMAC, a scale including 3 dimensions: pain, joint stiffness, and daily life ability to estimate joint function) score for knee and comorbidity; intra-operative items: surgery time, anesthesia time and tourniquet time.

Clinical Outcomes

NRS at rest (defined as the pain lying supine in bed) and in motion (defined as the most severe pain during passive motion and active exercise) were measured at 24 hours, 48 hours, 7 days and 6 months post-operatively; frequency and dose of rescue analgesic agents used during PCA were recorded; the surgical knee flexion were assessed at 7 days and 6 months post-operatively; anesthesia-related adverse events including incomplete analgesia at rest and in motion (defined as NRS for pain ⩾4 before rescue therapy), over-sedation, nausea and vomiting, respiratory depression, muscle weakness, and CFNB-related adverse events including catheter dropout, local infection and hematoma of CFNB catheter; postoperative length of hospital stay (defined as the interval between surgery and discharge) were recorded; WOMAC score for knee function, and quality-adjusted life years (QALY, a scale in which death has a value of 0 and optimal health has a value of 1 to adjust each year of life for the health-related quality of life experienced, always is transformed from EuroQol-5D score) converted from the EQ-5D score (EuroQol-5D score, a scale includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which were used to evaluate the quality of life) were assessed at 6 months after surgery.

Cost of PCA Analgesia

Cost in the PCIA group included the cost of drugs, pump devices, And cost in the CFNB group included the cost of drugs, pump devices and positioning the femoral nerve catheter (nerve stimulator and ultrasound equipment).

Direct cost: The direct medical cost in-hospital included the cost of medications, medical examinations, physical rehabilitation, nursing, and treating adverse events during hospitalization.

Indirect cost: The indirect cost was calculated as multiplying lost working days by the average daily income. The working days lost were defined as the interval between the beginning of hospital admission and the end of postoperative rehabilitation (8, 9).

Total cost: The total cost included direct medical cost and indirect cost.

The cost of hospitalization was based on the database of the Health Information Center of the First Affiliated Hospital of Chongqing Medical University. The average daily income was based on the database of Chongqing Municipality bureau.

Cost-Effectiveness Analysis and Cost-Utility Analysis

Cost-effectiveness analysis: The cost-effectiveness ratio (CER) of an intervention is calculated as the cost of the intervention divided by its effectiveness (10).

The PCIA or CFNB analgesic CER was calculated as dividing all of patients' PCA analgesic cost by the effectiveness of analgesia. The effectiveness of analgesia was evaluated as complete analgesia (100% minus the incidence of incomplete analgesia). The total CER was calculated at 6 months after surgery as dividing all of patients' total cost by the degree of joint function improvement defined as △WOMAC scores (calculated as pre-operative WOMAC scores minus post-operative WOMAC scores) (8-12).

Cost-utility analysis: The cost-utility ratio (CUR) of an intervention is the ratio of the cost of the intervention to the utility it produces in terms of the number of years lived in full health by the beneficiaries. Utility needs to be expressed by the QALY score converted from EQ-5D score for evaluating the quality of life. The CUR in our study was calculated as dividing the cost by the degree of quality of life improvement defined as △QALY score (calculated by post-operative QALY score minus pre-operative QALY score) of each patient.

The incremental cost-effectiveness ratio (ICER) is the ratio of the difference in cost and the difference in effect of two interventions. The ICER may be stated as (C1-C0)/(E1-E0) (C0 and E0 represent the cost and effect of one intervention, C1 and E1 represent the cost and effect of the other intervention) (7). In our study, C1 and E1 represented the cost and △QALY of the CFNB group, C0 and E0 represented the cost and △QALY of the PCIA group. The ICER indicated that cost needed to pay of the CFNB group to get one more QALY compared to PCIA group. Then ICER was compared to the cost effectiveness threshold to assess cost effectiveness. For example, $30,000 per QALY is suggested as a threshold ICER for a cost-effective intervention. Thus, any health intervention which has an incremental cost of more than $30,000 per additional QALY gained is likely to be rejected and any intervention which has an incremental cost of less than or equal to $ 30,000 per extra QALY gained is likely to be accepted as cost-effective(8-12).

Statistical Analysis

Sample calculation was based on the analgesic ef-

Table 1. Baseline Characteristics of Eligible Patients*.

Parameters	CFNB (N=140)	CFNB (N=140)	P value
Age (yr)	66.8±9.4	66.8±9.4	0.323
Height (cm)	158.2±7.7	158.2±7.7	0.240
Weight (kg)	63±8.4	63±8.4	0.847
Gender			
M/F	38/102	38/102	0.156†
ASA Grade			
Ⅰ	19	19	0.324†
Ⅱ	59	59	0.220†
Ⅲ	62	62	0.631†
NRS for knee	5 (4-5)	5 (4-5)	0.494‡
WOMAC score for knee	53 (51-56)	53 (51-56)	0.212‡
Operation time (minutes)	87.2±34.2	87.2±34.2	0.216
Anesthesia time (minutes)	125.7±32.6	125.7±32.6	0.235
Tourniquet time (minutes)	60.4±29.2	60.4±29.2	0.284

*Continuous variables were described as means ± SD or median(quartile), categorical variables as number of event(N). †Chi square test was used; ‡Wilcoxon test was used; the rest of parameters were compared using independent t-test. Statistical significance was considered when P value<0.05.

ficacy in a pilot study, a 10% difference between PCIA and CFNB on the incidence of moderate-severe pain in motion at 3 months after the surgery. Considering the dropout rate of 15% and statistical power of 80% at the 0.05 significant level, 280 patients estimated were randomly divided into the CFNB group and the PCIA group as 1:1 ratio.

The normality test was performed for measuring data. Normally distributed continuous variables were expressed as means ± SD, and Student's t-test was used for statistical analysis. Non-normally distributed variables were represented as median (quartile), and Wilcoxon test was used for comparison between groups. Categorical variables were represented by frequency (percent), and chi-square test was used for comparison between groups. Fisher' s exact test was used for categorical variables when the number of events was less than 5. Both intention-to-treat analysis (ITT analysis) and per-protocol set analysis (PPS analysis) were used in this study. ITT analysis was used in baseline characteristics (e.g.: age, ASA grade, NRS, WOMAC score); surgery time, anesthesia time and tourniquet time; and pre-operative conditions (hypertension, coronary artery disease). PPS analysis was used in other indicators. Statistical difference was assumed when P value <0.05. SAS 9.2 software was used for data analysis.

RESULTS

A total of 304 participants undergoing TKA were enrolled in this study. 24 patients were excluded for not meeting inclusion criteria or refusing to participate. The remaining 280 patients were included and randomized into CFNB group (N=140) and PCIA group (N=140), 13 patients in the CFNB group and 17 patients in the PCIA group withdrew from the study due to personal reasons or violation of study requirements, thus the remaining patients were used for PPS analysis of short-term clinical outcomes and corresponding costs. 18 patients in the CFNB group and 21 patients in the PCIA group were lost to follow-up, thus 109 patients in the CFNB group and 102 patients in the PCIA group were included for PPS analysis of long-term clinical outcomes and corresponding costs. There were no significant differences between the groups in baseline characteristics (e.g.: age, ASA grade, NRS, WOMAC score). Surgery time, anesthesia time and tourniquet time were also comparable in both groups (Table 1). Hypertension, coronary artery disease, COPD and diabetes were common pre-operative conditions in both groups (Table 2).

Pain Score and Rescue Analgesia

NRS at rest or in motion were similar at 24 hours and 48 hours post-operatively during the rescue analgesic period (Table 3). Accordingly, patients in the group PCIA required more analgesic bolus and frequency of rescue analgesia. Meanwhile, two types of rescue analgesic medications (parecoxib and tramadol) were consumed more often than those in the group CFNB (Table 4). On the 7 days, patients in the group CFNB showed significantly reduced pain in motion and at rest compared with that of group PCIA. Similarly, patients in the CFNB group reported less pain in motion and at rest when assessed at 3, 6 months after surgery (Table 3).

Knee Flexion and WOMAC Score

In two groups, knee flexion and WOMAC scores were comparable before surgery. Patients in the CFNB group showed slightly improved knee flexion at 7 days and 6 months post-operatively (Figure 1); WOMAC score in the CFNB

Table 2. Pre-operative Conditions of Enrolled Patients*.

Pre-operative condition	CFNB (N=140)	PCIA (N=140)	P value
Cardiovascular system	N (%)	N (%)	
Hypertension	41 (34.2)	29 (24.2)	0.098
Coronary artery disease	7 (5.8)	7 (5.8)	1.000
Arrhythmia			
Atrial fibrillation	1 (0.8)	1 (0.8)	1.000†
Ventricular premature	0 (0)	3 (2.5)	0.247†
Sinus bradycardia	0 (0)	2 (1.7)	0.498†
Respiratory system			
Asthma	2 (1.7)	0 (0)	0.498†
COPD	4 (3.3)	8 (5.7)	0.238†
Respiratory failure	1 (0.8)	1 (0.8)	1.000†
Urological system			
Renal syndrome	0 (0)	1 (0.8)	0.500†
Renal failure	0 (0)	1 (0.8)	0.500†
Endocrine system and Autoimmune disease			
Diabetes	18 (15)	9 (7.5)	0.068
Rheumatoid arthritis	0 (0)	3 (2.1)	0.247†
Thromboembolic events			
Cerebral embolism	2 (1.7)	0 (0)	0.498†
Myocardial infraction	0 (0)	0 (0)	
Venous thrombosis	0 (0)	2 (1.7)	0.498†
Peripheral artery embolism	0 (0)	0 (0)	

*Categorical variables were represented by frequency (percent) and Chi square was used. †Events less than 5 were compared with Fisher's exact test.

and PCIA group were 18(16-22) and21(17-24) at 6 months post-operatively; the change of WOMAC score (defined as minus in the figure 2 calculated as WOMAC score-preoperative minus WOMAC score-postoperative) was slightly higher in the CFNB group than that of the PCIA group (Figure 2). The mean post-operative length of stay in the CFNB group was 8.6 ± 2.8 days, which lower than 10.0 ± 2.3 days in the PCIA group.

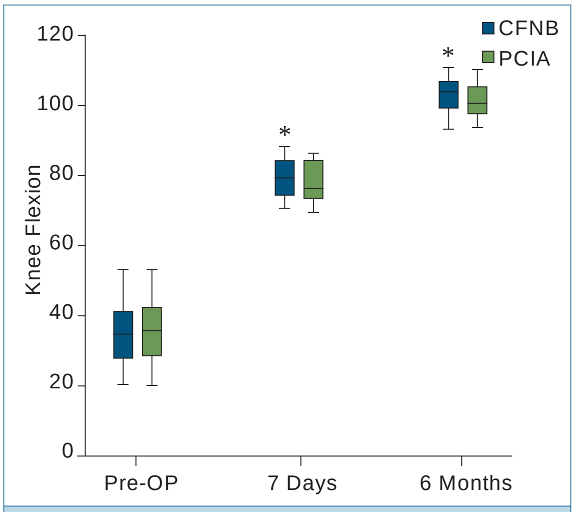

Figure 1. Knee Flexion Before and After Surgery. *A significant difference between group CFNB and PCIA, $P<0.05$. CFNB for continuous femoral nerve block, and PCIA for patient-controlled intravenous analgesia.

Analgesia Related Adverse Events

For patients in the CFNB and PCIA group, the reported incidence of incomplete analgesia in motion was 7.08% (N=9) and 17.07% (N=21) respectively; the incidence of over-sedation, nausea and vomiting, respiratory depression and muscle weakness were similar in both groups; no patients in the CFNB group reported catheter dropout, local hematoma or infection of catheter (Table 5).

Quality-Adjusted Life Year (QALY)

In both groups, pre-operative QALY scores were comparable. The QALY in the CFNB and PCIA group were 0.82 ± 0.06 vs 0.79 ± 0.06 at 6 months post-operatively. The change of QALY score (defined as minus in the figure 3 calculated as QALY score-postoperative minus QALY score-preoperative) in the CFNB group was slightly

Table 3. Numerical Rating Score (NRS) during Hospitalization and at 6 Months Post-Operatively[*].

Time points	CFNB	PCIA	P value
NRS in motion			
24 hours post-operatively	3 (3-4)	3.5 (3-4)	0.262
48 hours post-operatively	3 (3-4)	3 (3-4)	0.143
7 days post-operatively	3 (3-4)	4 (4-4)	<0.0001[†]
3 months post-operatively	3 (2-4)	3 (3-4)	0.021[†]
6 months post-operatively	3 (2-3)	3 (3-4)	0.011[†]
NRS at rest			
24 hours post-operatively	3 (3-4)	3 (3-4)	0.211
48 hours post-operatively	3 (3-4)	3 (3-4)	0.297
7 days post-operatively	3 (2-3)	3 (3-3)	0.031[†]
3 months post-operatively	1 (1-2)	2 (13)	<0.001[†]
6 months post-operatively	1 (1-1)	2 (1-2)	<0.0001[†]

[*]Continuous variables were described as median(quartile) and Wilcoxon test was used, [†]P value<0.05. For in-hospital pain evaluation the total number of patients in CFNB group was 127 and in PCIA group 123, while 109 patients in CFNB group and 102 in PCIA group were included to analyse pain at 6 months after surgery.

Table 4. Frequency and Medication Dose of Rescue Analgesia during PCA[*].

Analgesic outcomes	CFNB (N=127)	PCIA (N=123)	P value
Frequency of rescue analgesia	0 (0-1)	1 (0-2)	0.026
Frequency of analgesic pump bolus	2.3±0.8	2.7±0.7	0.0003[†]
Mean dose of rescue analgesic medications			
Parecoxib (mg)	0 (0-40)	40 (0-80)	0.049
Tramadol (mg)	0 (0-0)	0 (0-0)	0.000
Pethidine (mg)	0 (0-0)	0 (0-0)	0.150

[*]Continuous variables were described as mean ± standard deviation (SD) or median(quartile). [†]Independent t-test was used, the rest of parameters were compared with Wilcoxon test, statistical significance was considered when P value<0.05.

higher than that of PCIA group. However, there was no significant difference of the change of QALY score between group CFNB and PCIA (Figure 3).

The Cost of PCA Analgesia and Total Cost

The cost of PCA analgesia in CFNB and PCIA group were $149.8 vs $77.6 (Figure 4). However, the direct medical cost during hospitalization in CFNB and PCIA group were $9018.7 vs $9844.2, and the total cost in CFNB and PCIA group were $9234.2 vs $10236.7 (Figure 5).

Cost-Effectiveness Ratio (CER), Cost-Utility Ratio (CUR) and Incremental Cost- Effectiveness Ratio (ICER)

Patients in the CFNB group reported more PCA analgesic cost but higher percentage of complete analgesia, and PCA analgesic CER was higher than that of PCIA group. However, total CER of the CFNB group at 6 months post-operatively was obviously less than that of PCIA group (Table 6). The same trend was observed in CUR; patients in the CFNB group required more PCA analgesic cost but less total cost at 6 months post-operatively to obtain one QALY score (Table 7). Compared with PCIA group, patients in the CFNB group required $1,720 dollars (in 2015, 1 dollar≈6.3877 RMB, RMB is currency name in China) more PCA analgesic cost to obtain one more QALY, while the total ICER was negative value (Table 7).

DISCUSSION

As with other countries, the rapidly increasing healthcare cost is a critical issue in China. Therefore, physicians are paying more attention on patients' medical cost while ensuring clinical effectiveness. Meanwhile, government is using tools from economics to comprehensively evaluate clinical techniques to improve the efficiency of resource allocation and utilization (10). As one symbolic example of major surgeries in China, TKA is showing a steady increase annually. Post-operative analgesia plays one of the pivotal roles in surgical success and joint function recovery, yet few investigations have focused on the impact of post- operative analgesia on the long-term clinical outcomes, let alone to say, their economic differences (13, 14). In clinical, we usually use PCIA, epidural analgesia and CFNB which owns different features. Lee et al. (15) found that PCIA provided less better analgesia and more side effects such as nausea and sedation compared with continuous peripheral block. Patel et al. (16) found peripheral nerve block was safe with a significant decrease in postoperative complications and provided adequate pain relief compared to epidural anesthesia

CFNB and PCIA are two commonly used methods for postoperative analgesia after TKA. Our study showed that CFNB could achieve satisfactory clinical outcomes during hospitalization (PCIA: N=123, CFNB: N=127) and at 6 months postoperatively (PCIA: N=102, CFNB: N=109) on the basis of relatively low total cost, in which part of analogous data was also observed in many other researches (17-21).

In the present study, we found patients in the CFNB group had better NRS and improved knee flexion at 7 days (PCIA: N=123, CFNB: N=127) and 6 months (PCIA: N=102, CFNB: N=109) post-operatively, with the same NRS at 24 hours and 48 hours after surgery but less rescue analgesic medications (PCIA: N=123, CFNB: N=127) were used compared with PCIA, suggesting that CFNB is superior to control acute pain and the development of chronic pain. Singelyn et al. (22) found IV PCA with morphine and CFNB provided similar pain relief and hip flexion, but CFNB was associated with less side effects in patients undergoing total hip arthroplasty. The discrepancy may due to the differences of operation region, in which knee joint needs much more exercise with better analgesia. The prominent finding of our study was that patients in the CFNB group had improvement both in WOMAC and QALY score, meanwhile required less total cost during 6 months follow-up (PCIA: N=102, CFNB: N=109), suggesting that CFNB analgesia is cost effective for patients undergoing TKA.

In this study, we used three commonly applied tools from health economics including the CER, CUR, and ICER to evaluate the economic performances of CFNB and PCIA (7, 8). In order to objectively evaluate the economic differences of two analgesic methods, we divided the cost into the cost of PCA analgesia and the total cost. The cost of CFNB analgesia was higher than that of PCIA, because CFNB was required to position the femoral nerve using a nerve stimulator and an ultrasound device. Accordingly, the analgesic CER of CFNB was higher than that of PCIA. However, our study showed that CFNB could provide more satisfactory analgesia with higher rate of complete analgesia compared with PCIA (PCIA: N=123, CFNB: N=127), subsequently decreasing the need for administration of rescue analgesia with their expenditure. With better analgesia, knee function of patients was improved significantly at 48 hours, 72 hours, and 7 days after surgery in the CFNB group (PCIA: N=123, CFNB: N=127) (23). Early improvement in joint function may reduce long- term rehabilitation, medications,

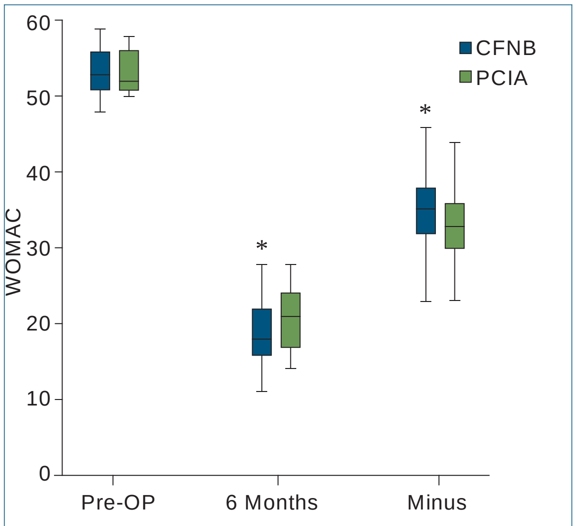

Figure 2. WOMAC Score Before and After Surgery.
*P value<0.05. WOMAC was the abbreviation for Western Ontario and McMaster Universities, CFNB for continuous femoral nerve block, and PCIA for patient-controlled intravenous analgesia. Minus defined as the change of WOMAC score (calculated as WOMAC score- preoperative minus WOMAC score- postoperative).

Table 5. Adverse Events Related to Analgesia.

Items	CFNB (N=127)	PCIA (N=123)	P value
Incomplete analgesia			
In motion	9 (7.08)	21 (17.07)	0.015
At rest	0 (0)	0 (0)	—
Over-sedation	2 (1.57)	5 (4.06)	0.275†
Nausea and vomiting	3(2.36)	4 (3.25)	0.719†
Respiratory depression	0 (0)	2 (1.62)	0.149†
Muscle weakness	4 (3.14)	1 (0.81)	0.370†
Catheter dropout	0(0)	0(0)	—
Local thrombosis	0(0)	0(0)	—
Local infection	0(0)	0(0)	—

*Categorical variables were represented by frequency (percent) and Chi square was used. †Events less than 5 were compared with Fisher's exact test. Statistical significance was considered when P value<0.05.

and nursing cost (24, 25). Our research showed that the length of stay and consequently the total hospital cost decreased markedly (PCIA: N=123, CFNB: N=127). Researchers also found that compared with IV opioids for TKA analgesia, using epidural or CFNB for 48 to 72 hours could shorten hospitalization length- of- stay from 50 to 40 days (France), 21 to 17 days (Belgium) and 5 to 4 days (United States) (20). The intensity of postoperative pain is a risk factor for chronic pain after TKA (26). We found pa-

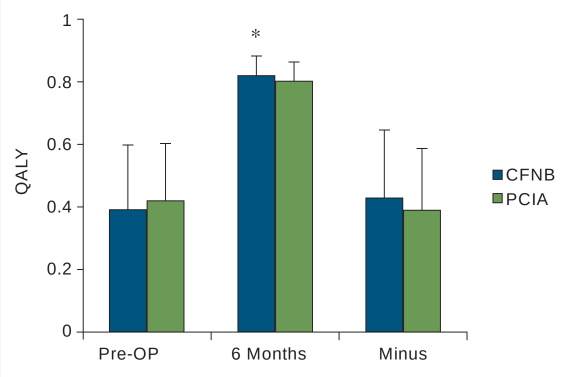

Figure 3. QALY Score Before and After Surgery. *P value<0.05. QALY was the abbreviation for quality-adjusted life years, CFNB for continuous femoral nerve block, and PCIA for patient-controlled intravenous analgesia. Minus defined as the change of QALY score (calculated as QALY score-postoperative minus QALY score-preoperative).

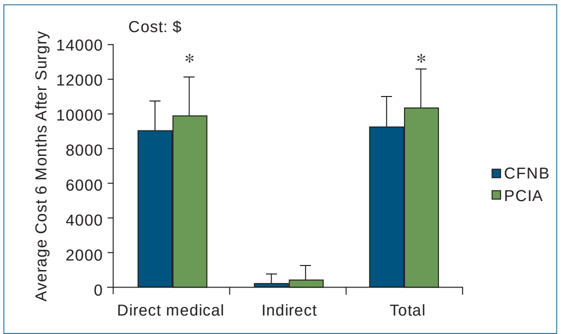

Figure 5. Average Cost During Hospitalization and at 6 months After Surgery. *A significant difference between group CFNB and PCIA, P<0.05. Direct medical cost was defined as all in-hospital cost; indirect cost was defined as patients' lost wages because of illness; total cost included direct medical cost and indirect cost. CFNB for continuous femoral nerve block, and PCIA for patient-controlled intravenous analgesia.

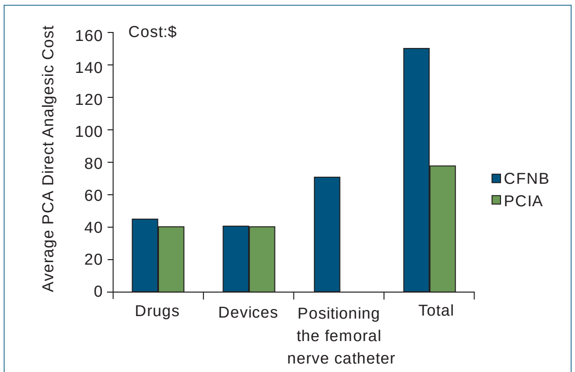

Figure 4. Average Direct PCA Analgesic Cost. Drugs were defined as ropivacaine in group CFNB and tramadol, flurbiprofen axetil, dexamethasone in group PCIA; Devices were defined as PCA pump in both groups; positioning the femoral nerve catheter were defined as ultrasound consumables and nerve stimulator in group CFNB; total analgesic cost of PCA included drugs, devices, positioning the nerve catheter in the group CFNB and drugs, devices in the group PCIA. CFNB for continuous femoral nerve block, and PCIA for patient-controlled intravenous analgesia.

tients in the CFNB group displayed lower NRS at 6 months (PCIA: N=102, CFNB: N=109), patients with controlled chronic pain could begin appropriate joint functional exercise earlier, therefore, these patients could return to normal social activities faster with corresponding reduction of indirect cost. So its total CER was much less than that of the PCIA group, suggesting the function- enhancing and cost- effectiveness role of regional analgesia as continuous femoral nerve block in patients receiving TKA. Ilfeld et al. (20) reported the average per- patient total hospitalization cost undergoing TKA with CFNB was $7,974, which was lower than that in our study, and it maybe attribute to 5 days longer length of stay in hospital in our study.

The CUR can be used to analyze the quality and quantity of life comprehensively, and it does not just take a delimited clinical outcome as the final indicator (8- 10). In the present study, we used QALY as the indicator of utility. QALY is a measure of disease burden, including both the quality and the quantity of life lived (27). It is used to assess the monetary value of a medical intervention. QALY score can be converted from the EQ-5D score, which is the most widely used scale for evaluating the quality of life and, as noted, includes 5 dimensions: mobility, self- care, usual activities, pain/discomfort, and anxiety/depression (28-29). We found that in both groups the quality of life improved after surgery. However, 6 months after surgery, pain was relieved more obviously and the recovery of joint function was quicker in the CFNB group (PCIA: N=102, CFNB: N=109). So patients in this group could return to social activities earlier, with improvement in mood, social ability and satisfaction. Although the analgesic CUR of CFNB was slightly higher, the total CUR of CFNB was significantly lower (PCIA: N=102, CFNB: N=

109). The PCA analgesia cost required to obtain an increase of 1 QALY in the CFNB group was $938 dollars more than that of PCIA group, yet the total cost for an increase of 1 QALY was less than that of PCIA group, suggesting that optimizing post-operative analgesia was cost-effective in improving surgical prognosis for TKA patients (PCIA: N=102, CFNB: N=109). The incremental cost-effectiveness ratio (ICER) can be used to calculate payments the society needs to have to get one more QALY compared with other treatments. Then ICER was compared to the cost effectiveness threshold to assess for cost effectiveness (30). However, there is no specific cost effectiveness threshold for TKA in our country. Our study showed that compared to the PCIA group, the ICERs of PCA analgesia cost and total cost in CFNB group were $1,720 dollars and negative value, respectively (PCIA: N=102, CFNB: N=109), which indicated that CFNB is a cost-effective analgesia that could achieve relatively high QALY using less money (8-10).

In the present study, we observed the effects of CFNB on short-term and long-term clinical outcomes of patients after TKA, including joint function and quality of life, together with the economic characteristics of alternative anesthetic treatments, and comprehensively evaluated the advantages of CFNB vs PCIA. However, our study still has some limitations as follows: The direct non-medical cost and intangible cost were not calculated, therefore the total cost may be underestimated; Without sensitivity analysis, and the results had a certain degree of uncertainty; The follow-up period was only 6 months after surgery, and the effects of two analgesic methods on long-term clinical outcomes and economics after TKA should be further studied. More importantly, rate of complete analgesia, WOMAC score and QALY score were secondary outcomes in this study and thus do not have the statistical strength for primary outcomes. However, this preliminary study still revealed promising outcomes of CFNB both clinically and economically compared to traditional intravenous analgesia.

Table 6. Cost Effectiveness Ratio (CER) for Different Analgesic Methods*.

Items	CFNB	PCIA
Analysis of PCA analgesic cost		
Cost of PCA analgesia ($) †	19,025	9,541
Rate of complete analgesia‡	118 (92.92)	102 (82.93)
PCA analgesic CER($) §	205	115
Analysis of total cost		
Total cost ($) ‖	1,006,525	1,044,148
△WOMAC (score) ¶	3,761	3,326
Total CER($)**	268	314

*Categorical variables were represented by frequency (percent); The total number of patients was 127 in CFNB group and 123 in PCIA group for PCA analgesic CER evaluation, while 109 patients in CFNB group and 102 patients in PCIA group were included in the analysis of total CER. † Defined as the sum of PCA analgesic cost of all patients in group CFNB and that in group PCIA. ‡Defined as the percentage of complete analgesia. §Defined as PCA analgesic cost needed to obtain 1% complete analgesia. ‖Defined as the sum of total cost including direct medical cost and indirect cost of all patients in group CFNB and that in group PCIA. ¶Defined as total sum of △WOMAC score (i.e. pre-operative WOMAC score minus post-operative WOMAC) of all patients of group CFNB and PCIA. ** Defined as total cost needed to decrease one WOMAC score.

Table 7. Cost-Utility Ratio (CUR) and Incremental Cost-Effectiveness Ratio (ICER) for Different Analgesic Methods*

Items	CFNB (N=109)	PCIA (N=102)	P value
Analysis of Analgesic Cost			
△QALY (scores) †	0.4±0.2	0.4±0.2	0.148
PCA analgesic CUR ($)‡	436±186	249±99	<0.01
PCA analgesic ICER ($)§	1,720	—	
Analysis of Total Cost			
△QALY (scores) †	0.4±0.2	0.4±0.2	0.148
Total CUR ($)‖	26,652±12,068	32,593±15,112	<0.01
Total ICER ($)¶	Negative value	—	

*Continuous variables were described as means ± standard deviation (SD) and independent t-test was used, statistical significance was considered when P value<0.05. †Defined as post-operative QALY score minus pre-operative QALY. ‡Defined as PCA analgesic cost needed to obtain one QALY score. §Defined as PCA analgesic cost needed to obtain one more QALY score of CFNB group and group PCIA. ‖Defined as total cost needed to obtain one QALY score. ¶Defined as total cost needed to obtain one more QALY score of CFNB group and group PCIA.

CONCLUSION

Post-operative analgesia constitutes one of the important dimensions ensuring surgical recovery. With rigorous analgesic rescue therapy, the implementation of CFNB facilitated post-operative analgesia (PCIA: N=123, CFNB: N=127), earlier recovery of joint function in patients receiving TKA compared with intravenous analgesia (PCIA: N=102, CFNB: N=109). The patients in the CFNB group showed improved cost-effectiveness and cost-utility, which means that patients receiving CFNB with rigorous rescue analgesia could cost less money, reduced economic burden of family and saved medical resources in nation. Meanwhile, it may not only reduce financial cost from a societal perspective, but increase other patients' quality-of-life by decreasing the often long wait for joint replacement.

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