Evaluation of the feasibility of dexamethasone added to bupivacaine for continuous femoral nerve block for postoperative analgesia and rehabilitation after reconstructive knee surgery.

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Abstract
Achieving adequate analgesia after total knee arthroplasty (TKA) can be a challenging; femoral nerve block (FNB) has been investigated and found to improve pain control following TKA. mixing local anaesthetic with adjuvant drugs improve the quality of analgesia from peripheral nerve blocks. We hypothesized that; adding dexamethasone to bupivacaine for continuous femoral nerve block provides better peri-operative analgesia than standard CFNB. Patients & methods: 150 patients affected by osteoarthritis scheduled for primary unilateral TKA were enrolled in the study. Patients were allocated into 3 groups, FNBD, FNB, and a control group. The following parameters were measured; total amount of morphine consumed, NRS, at rest and during movement, satisfaction scores for patient, sergeant, and anesthesia resident. Results: Patients in FNBD Group reported lower pain scores on passive movement compared to FNB Group. Cumulative morphine consumption was lower in FNBD Group after recruitment. Conclusion: Dexamethasone added to bupivacaine prolonged analgesia from FNB. Further studies will be necessary to demonstrate its safety for perineural use.

Introduction
randomized, single-blinded, controlled study was to compare the effectiveness and feasibility of adding dexamethasone to bupivacaine for CFNB. We hypothesized that; adding dexamethasone to bupivacaine for CFNB provides better peri-operative analgesia than standard CFNB. The primary endpoints were the duration of analgesia, defined as the interval between the onset of sensory block and the initial use of opioid analgesia for surgical site pain. The amount of morphine required in the first 24 hours and the comparison of the total amount of morphine used, the onset time and duration of motor and sensory blocks. As a secondary outcome, numeric rating scores (NRS) for pain were assessed at rest and passive movement, 30 minutes after the end of the operation and regularly for the next 72 hours, and cost-effectiveness. Satisfaction with the analgesic regimen received was measured at the end of the assessment.

Materials and Methods
After the approval of research ethic committee, One hundred fifty patients suffering from osteoarthritis scheduled for primary unilateral TKA were enrolled in the study. The inclusion criteria were; ASA grades I to III, and age above 50 years. Exclusion criteria were patient refusal, contraindication to regional anesthesia, American Society of Anesthesiologists status (ASA) IV or V, peripheral neuropathy, acute intercurrent heart disease; chronic opiate use, and known allergic reaction to local anesthetics, paracetamol or morphine; skin lesions/infection at
level of anesthesia, the LMA was introduced. A Size 4 was used for patients weighing up to 90 kg and Size 5 was used for patients more than 90 kg. The LMA was inflated with a maximum of 25 ml of air, was then connected to the breathing system; patient was allowed to breathe spontaneously. Sevoflurane was titrated to maintain adequate depth of anesthesia. At the end of procedure, anesthetic gases were discontinued, supraglottic device was removed. When patient showed adequate recovery from anesthesia, patients transferred to the recovery room where close observation of hemodynamic parameters was detected. In case of intra-operative increase in hemodynamic parameters IV remifentanil infusion was started at 0.1 mg/kg/min. Standard monitoring (pulse oximetry, ECG, non-invasive arterial pressure, end-tidal capnograph, and end-tidal anesthetic concentration) was done. On arrival to the post-anesthesia care unit, all patients received a patient controlled analgesia (IV-PCA) system, which provide 1 mg of morphine on demand with block out interval of 20 minutes and a maximum 6 hour dose of 10 mg. For determination of feasibility, time to perform the procedure, a number of attempts, and complications were measured and recorded based upon a subjective 4-point scale rating (1: easy, 2: average, 3: difficult, 4: very difficult). The average time to obtain an adequate block was collected. To determine effectiveness of pain control, numerical rating scores were assessed at baseline, immediately after the end of the procedure, and at 15 minutes, 30 minutes, 60 minutes, and regularly after the procedure for 72 hours. An examination of sensory level to cold temperature and motor block in the femoral nerve distribution was established. Motor blockade was estimated using a modified Bromage scale (0-no blockade: extended limb lift off the bed; 1-flexion/ extension at the knee and ankle joint; 2-no flexion/extension of the knee or ankle joint; and 3-complete blockade).

Postoperative Pain Management
Nursing staff was instructed to use a numerical rating scale (NRS) score of 3 or more to define an endpoint for administering morphine. Data collected at 1, 2, 4, 6, 12, 24, 48, and 72 h postoperatively. Data included minimum interval systolic blood pressure and oxygen saturation. Morphine consumption and any other medications were also recorded. NRS scores were obtained at rest and with movement. While in the PACU, patients could receive supplemental IV morphine to achieve satisfactory analgesia as defined by the individual patient. All patients received regular postoperative analgesia, comprising paracetamol 1 g i.v. four times daily. Ondansetron 4 mg was prescribed for nausea or vomiting treatment, when required. Subcutaneous enoxaparin 4000 IU daily was prescribed as deep venous thrombosis prophylaxis. Two hours after recovery, the patients left the post-anesthesia care unit.

Assessment and Data Collection
The primary endpoints of the study were the amount of morphine required in the first 24 hours and the total amount of morphine used in the three studied groups. Secondary endpoints were NRS score in the three studied groups during the postoperative 72 h, the incidence of side effects block site; and renal dysfunction. Patients with systemic infections. After obtaining written informed consent, patients were allocated to one of three groups. The femoral nerve block with dexamethasone added to bupivacaine for femoral nerve block (FNB-D), group A, the standard femoral nerve block (FNB) group B, and the control group C, using a sealed envelope, prepared before the study, in conjunction with a computer-generated randomization list. All patients enrolled in the study receive general anesthesia; that was implemented after the block in group A, and B patients. Multi-parametric monitoring; including electrocardiogram, pulse oximetry, end tidal carbon dioxide, and non-invasive blood pressure was started. Intravenous (IV) access was obtained and IV infusion was started using hydroxyethyl starch (HES 130/0.4) solution. Vital signs were recorded during the maneuver. In the receiving area all patients received IV premedication.

Trial Interventions
Continuous femoral nerve block technique: As regards group A, and B the block was performed in the block room before pushing into the operating room. Premedication was done using 1 mg dormicum + 50 µg fentanyl. The skin of the anterior thigh was prepared aseptically and a sterile drape was placed. The skin was anesthetized using a 22 G needle and 1% lidocaine. The inguinal area was scanned using a high resolution ultrasound device (Sonosite, probe, transducer with a frequency of 5-10 MHz). After examination of the anatomy of the femoral artery and vein, the femoral nerve was located 1 cm laterally to the femoral artery. The block needle was attached to a nerve stimulator. The first target point was direct visualization of the needle tip maintained with ultrasound while inserting the needle, until optimal positioning of the needle tip was achieved. The second target used for injection was an ipsilateral quadriiceps contraction (patellar movements) at 0.5 am, (stimulator frequency at 2 Hz and a pulse width of 0.1 s). On attaining this endpoint the needle was immobilized, and following negative aspiration 25 ml of 0.5% bupivacaine +8 mg dexamethasone were injected slowly in group A patients, and 25 ml of 0.5% bupivacaine was injected slowly in group B patients; During the injection the spread of the local anesthetic solution within the facial space was visualized. The cannula was then advanced over the needle, the needle withdrawn and the catheter placed through the cannula 3 - 4 cm in cephalad direction. Finally, the cannula was removed and the catheter secured to the skin using an adhesive, transparent dressing. A continuous infusion of 0.25% bupivacaine was started at a rate of 4 ml per hour, after the end of the operation, infusion starting time that was correlated with first time patient reported pain after the end of the procedure was documented, and infusion was continued for 72 hours delivered via an elastomeric pump.

Anesthesia induction
For all patients enrolled in the study; general anesthesia was carried out with fentanyl (1 - 2 µg kg–1 to a maximum dose of 100 µg i.v. and , propofol (2 - 3 mg kg–1). After the establishment of the deep
The required sample size was calculated using a G*Power® software version 3.1.0. The primary endpoints were the duration of analgesia, defined as the interval between the onset of sensory block and the initial PACU use of opioid analgesia for surgical site pain; the amount of morphine required in the first 24 hours and the comparison of the total amount of morphine used. As a secondary outcome NRS, cost-effectiveness, and patient satisfaction scores were evaluated in the studied groups. The dose of 8 mg was chosen because it has been used previously for perineural injection and is within the dose range used clinically for postoperative nausea. Since variables were on an ordinal scale we expected the data to be skewed. Therefore, we used the two-tailed Wilcoxon-Mann-Whitney test to estimate our sample size. Our study was powered to detect a 50% reduction in VAS pain score six hours after recruitment. Assuming a two-tailed α-error of 0.05, a β-error of 0.2, we estimated that a sample size of 50 patients in each group would have a power of 85% to detect an effect size (d) of 1.1. Data were analyzed on a personal computer using the Statistical Package for Social Sciences. Normality of quantitative data distribution was tested using the one-sample Kolmogorov-Smirnov goodness-of-fit test. Normally distributed quantitative data were presented as mean (standard deviation) and between-group differences were compared parametrically using the independent samples Student t test. Repeated measures were compared using repeated measures analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. Non-normally distributed quantitative data were presented as median (interquartile range) and inter-group differences were compared non-parametrically using the Mann-Whitney U test. Categorical data were presented as number (percentage) and intergroup differences were compared using the Pearson χ2-test with the application of Fisher's exact test when appropriate. All P values are two-tailed. P values < 0.05 were considered statistically significant.

(Fig. I, Tab. III). Similarly, Pain measured during passive movement was less in FNBD Group at each time point up to 48 hours after recruitment, showed statistically significant difference in comparison to the other two studied groups (Fig. II, Tab. IV). Morphine consumption is shown in Table (II). The FNBD group had a lower morphine consumption compared to FNB, and control groups. Average consumption within the first 6 hours was (0.78 ± 0.08 mg) in FNBD group compared to (4.06 ± 0.66 mg) in the FNB group; and (5.06 ± 0.30mg) in the control group. At 12 h, average morphine consumption was (2.08 ± 0.21mg) in FNBD group, vs (3.09 ± 0.18mg) in FNB group, and (5.12 ± 0.18mg) in the control group. At 24 h, average morphine consumption was (5.65 ± 0.17mg) in FNBD vs (9.12 ± 0.21 mg) in FNB and9. 14 ± 0.20mg at control group. It was clear that, Cumulative morphine consumption was lower in FNBD Group at each time point after (nausea, vomiting and respiratory depression), antiemetic requirements, surgeon satisfaction, anesthesia resident satisfaction, and patient satisfaction. Based on this the parameters recorded were: total volume of morphine used from the PCA pump, numerical rating pain score (NRS) from 0 (no pain) to 10 (worst pain imaginable) both at rest and on flexion of the operated knee, nausea (on a 4-point scale: 0, no nausea or vomiting; 1, nausea no vomiting; 2, vomiting; 3, persistent vomiting), level of sedation (1 _ fully alert, 2 _ drowsy when undisturbed, 3 _ consistently drowsy, 4arousable only with stimulation, 5 _ unarousable); nausea or pruritus requiring treatment; or any numbness or weakness in the operative leg, and motor power in the operated limb using the modified Bromage scale and ambulation. In addition, at each measurement interval, a sensory examination to cold temperature was performed to assess the presence or absence of residual femoral nerve block. The PCA was discontinued after 72 hours. Patients received regular physiotherapy from day 3 and were encouraged to exercise and walk with assistance as early as possible. Patients’ progress was recorded by the physiotherapists, nurses, and medical staff and was assessed for suitability for discharge from day 5. The response to physical therapy was assessed based on the following numeric scale, 1 = inappropriate, 2 = fair, 3 = good. Time to mobilization, and discharge was documented. After the operation, surgeon was asked to qualify the operative conditions according to the following numeric scale: 0 = unsuccessful, 1 = poor, 2 = acceptable, and 3 = perfect. Before discharge the patient also, was asked to rate the operative conditions according to the following numeric scale: excellent, 4 = no pain; good, 3 = minor pain with no need for supplemental analgesics; moderate, 2 = pain which required supplemental analgesic; and unsuccessful, 1 = patient did not tolerate regional anesthesia.

Study Design and Statistical Methods

Results

150 patients were enrolled in the study. They were allocated to groups before surgery. All femoral nerve blocks including insertion and securing the femoral nerve catheter were implemented in less than 13 minutes. All procedures required only one attempt; no complication was recorded during anesthetic procedures. Patient characteristics were similar between the 3 studied groups (Table I), with no statistically significant differences. All the blocks were feasible, and there were no cases of difficulty. Two patients in the FNBD, eight patients in FNB, and ten patients in the control group required intraoperative remifentanil (0.1 mcg/kg/min). No episodes of excessive sedation, respiratory depression or severe hypotension were reported. Pain as measured at rest was consistently less at all time points, reaching the statistical significance level 30 minutes, six, 12, 24, and 48 hours after recruitment.
recommended for reducing pain scores and providing supplemental analgesia. Recent studies reported that; FNB is effective to ensure a better post-operative analgesia (17). The effective reduction in neuroendocrine response to the surgical stress, induced by FNB, coupled with a lower sensitization of central nervous system. And a muscle spasm reflex to pain, optimizes knee mobilization, reducing the postoperative hospital stay and provide the optimum opioid sparing effect (18,19). Our team reported that; dexamethasone significantly prolongs the analgesic effect of plain bupivacaine in the FNBD group in comparison to the other two studied groups. This finding is supported by previous studies, but comparisons were difficult because of different local anesthetic mixtures used, different blocks studied, and different methods of evaluating the block duration. The block prolongation we demonstrated in our study was consistent with the data reported by . Vieira and colleagues, observed that; adding dexamethasone to a mixture of bupivacaine, clonidine, and epinephrine increased interscalene block duration from 14 to 24 h (20). The same finding were demonstrated by Parrington SJ et al. when dexamethasone was combined with mepivacaine for supraclavicular blocks (21). The safety profile of dexamethasone is promising. Still no studies reported neurotoxicity as regard dexamethasone. Animal studies demonstrated no long-term changes in nerve structure or function as regard local steroid administration (22). As regards toxicity that may result from the corticosteroids mechanism of action; it may result from the nature or the vehicle used in steroid preparation; which not the issue for dexamethasone (23). However, corticosteroids have been used safely in the epidural space for the treatment of radicular pain (24). Dexamethasone has been reported in many studies as an adjuvant to epidural local anesthetics (25). Based on the data reported, the neurological risk, of dexamethasone appears to be small; moreover; the use of dexamethasone as an adjunct to local anesthesia for nerve blocks is discussed in prominent textbooks (26,27). The limitation that faced our study reflected ethical and economic reasons, it was difficult to use a double-blinded methodology. It is considered to be ethically unacceptable to insert a placebo femoral nerve catheter for blinding purposes only. Outcomes such as postoperative respiratory or cardiovascular morbidities were not assessed. Conclusion Dexamethasone added to bupivacaine prolonged analgesia fromFNB, the combined effect of dexamethasone and bupivacaine produced 24 h of analgesia. In spite of the promising toxicity profile of dexamethasone, further studies will be necessary to demonstrate its safety for peripheral use.

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