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Post-operative analgesia following total knee arthroplasty: comparison of low-dose intrathecal morphine and single-shot ultrasound-guided femoral nerve block: a randomized, single blinded, controlled study

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Abstract. – *Background and Objectives:* **Total knee arthroplasty often results in marked postoperative pain. A recent meta-analysis supports the use of femoral nerve block or alternatively spinal injection of morphine plus local anaesthetic for post-operative analgesia. On the other hand, the use of intrathecal morphine may be associated with a large number of distressing side effects (itching, urinary retention, nausea and vomiting, delayed respiratory depression). The aim of this study was to compare the effectiveness of femoral nerve block and low dose intrathecal morphine in post-operative analgesia after primary unilateral total knee arthroplasty.**

Material and Methods: **Fifty-two consecutive patients scheduled for primary unilateral total knee arthroplasty were allocated to the intrathecal morphine group (ITM group) or to the femoral nerve block group (FNB group). In ITM group a subarachnoid puncture was performed at the L3-L4 inter-vertebral space with hyperbaric bupivacaine 15 mg plus 100 mcg of preservative-free morphine. Patients allocated to the FNB group received a single-injection ultrasound-assisted femoral nerve block with ropivacaine 0.75% 25 ml before the spinal injection of hyperbaric bupivacaine 15 mg. All patients received postoperative patient-controlled-analgesia (PCA) morphine, using a 1-mg bolus and a 5-minute lockout period. Data were analyzed using Student t test or two-way analysis of variance (ANOVA) for repeated measures with time and treatment as the 2 factors. Post hoc comparisons were performed by Bonferroni test. Statistical significance for all test was a *p* value <0.05.**

Results: **Patient characteristics were similar between the 2 groups. We found a statistically significant differences in postoperative pain between the two groups: ITM group had the lower visual analogic pain score (VAS) values. Morphine consumption was lower in the ITM group: average consumption within the first 6 hours was 0.9 mg in IT group compared to 3.1 mg in FNB group; at 12 h 4.2 mg vs 6.3 mg; at 24 h 6.9 mg vs 10.3 mg; at 48 h 9.7 mg vs 13.6 mg. However, the difference in the opiate consumption was not statistically different (*p* value =0.06). Thirteen patients in ITM group experienced itching, only 5 in FNB group. We did not find any difference in the two treatment groups in the use of antiemetic and antipruritic medication. No cases of respiratory depression was recorded.**

Conclusions: **Our results show that low dose of intrathecal morphine may be safe and more efficient than single-shot femoral nerve block for post-operative analgesia after total knee arthroplasty.**

Key Words:

Knee arthroplasty, Postoperative analgesia, Intrathecal morphine, Femoral nerve block.

Introduction

Total knee arthroplasty (TKA) is a commonly performed surgical procedure often characterized by marked post-operative pain despite the beneficial long-term effects. Patients are usually elderly with comorbid diseases. Because of that, an appropriate anaesthetic and analgesic regimen is

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mandatory to minimize adverse side effects as well as providing suitable pain relief. Optimal peri-operative analgesia will enhance functional recovery, including timely recovery of knee mobility, reducing postoperative morbidity[1,2]. Current approaches used for treatment of post-operative pain include systemic opiates, epidural analgesia and peripheral nerve blocks[1-5], although immediate anticoagulation may limit the options for epidural analgesia[1].

A recent meta-analysis supports the use of femoral nerve block for post-operative analgesia for primary TKA. Alternatively, there is solid evidence supporting the use of a spinal injection of local anaesthetic plus morphine[6]. Any technique, however, should be supplemented with paracetamol, conventional nonsteroidal anti-inflammatory drug (NSAID) or COX-2-selective inhibitors and gabapentinoids plus intravenous strong opiates for break-through high-intensity pain[6].

On the other hand, the use of IT morphine may be associated with a number of distressing side effects e.g. itching, urinary retention, nausea and vomiting, and potentially life threatening adverse effects as delayed respiratory depression[7].

The aim of this prospective randomized single-blinded study was to compare the effectiveness and feasibility of two analgesic techniques (femoral nerve block vs low dose intrathecal morphine) for post-operative analgesia after primary unilateral TKA.

Materials and Methods

The study was approved by our Research Ethic Committee. Fifty-two consecutive patients affected by osteoarthritis scheduled for primary unilateral bicompartmental-cemented TKA were enrolled in the study, signing a written informed consent.

Exclusion criteria were patient refusal, contraindication to regional anaesthesia, American Society of Anaesthesiologists status (ASA) IV or V, peripheral neuropathy, chronic opiate use, and known allergic reaction to local anaesthetics, paracetamol or morphine.

After obtaining written informed consent from all subjects, the patients was monitorized since in operating room with electrocardiogram, pulse oximetry, and non-invasive blood pressure monitoring; after then intravenous (IV) access was obtained. About 5 minutes before anaesthesia, all patients received IV premedication (midazolam 2 or 3 mg plus fentanyl 50 mcg) titrated to produce sedation while maintaining verbal contact. Intravenous fluids were commenced using Ringer lactate solution (5 ml/kg).

Vital signs were recorded during the manoeuvre. Patients were allocated to the intrathecal morphine group (ITM group) or to the femoral nerve block group (FNB group) using a sealed envelope, prepared before the study, in conjunction with a computer-generated randomization list.

The procedures were performed by a senior anaesthesiologist, highly trained in both techniques and not involved in the post-operative evaluation of the patients.

In ITM group the patients were placed in the sitting position and, after local anaesthesia of the skin (3 mL of lidocaine 2%), a subarachnoid puncture was performed with a 25-gauge Whitacre spinal needle at the L3-L4 inter-vertebral space. The correct placement was confirmed by free-flow aspiration of cerebrospinal fluid. Then, the administration of hyperbaric bupivacaine 15 mg plus 100 mcg of preservative-free morphine sulphate over 30 sec has been started.

Patients allocated to the second group (FNB group) received a single injection femoral nerve block before the intrathecal injection of hyperbaric bupivacaine 15 mg.

The inguinal area was scanned using a high resolution ultrasound device (Sonosite, L38e probe, 38 mm broadband linear array transducer with a frequency of 5-10 MHz, Bothell, WA, USA). After examination of the anatomy of the femoral artery and vein, the femoral nerve was located 1 cm laterally to the femoral artery and under the ileopectinal fascia. A 22-gauge B-bevel shaped needle was inserted 2 cm distal to the inguinal ligament with an angle of 30° and advanced toward the femoral nerve under stimulation (Stimuplex, B Braun, Bethlehem, PA, USA). Direct visualization of the needle tip was maintained with ultrasound while inserting the needle, until optimal positioning of the needle tip was achieved within the fascial space as close as possible to the femoral nerve. The second target used for injection was an ipsilateral quadriceps contraction (patellar movements) at 0.5 mA, (stimulator frequency at 2 Hz and pulse width of 0.1 s). At this point, 25 mL of 0.75% ropivacaine were injected slowly after negative aspiration. During the injection the spread of local anaesthetic solution within the fascial space was visualized. The injection was

stopped and the needle repositioned if the patient complained of pain during injection. The time and the difficulty to perform each block was recorded on a subjective 5-point scale rating (1: very easy, 2: easy, 3: average, 4: difficult, 5: very difficult). The average time to obtain an adequate block was collected. An evaluation of sensory level to cold temperature and motor block in the femoral nerve distribution was established before performance of the spinal anaesthesia. Motor blockade was estimated using a modified Bromage scale (0-no blockade: extended limb lift off the bed; 1-flexion/extension at knee and ankle joint; 2-no flexion/extension at knee or ankle joint; and 3-complete blockade). Once a complete block could be shown, spinal anaesthesia was performed.

In the operating theatre multi-parametric monitoring and IV infusion were continued, and in case of intra-operative discomfort IV remifentanil infusion were started at 0,1 mcg/kg/min.

All patients received regular postoperative analgesia, comprising paracetamol 1 g i.v. four times daily and i.v. ketorolac 30 mg 2 times every 24 h. All patients received patient-controlled-analgesia (PCA) morphine, using a 1-mg bolus and a 5-minute lockout period with no background infusion. Patients were instructed in the use of the PCA. 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-anaesthesia care unit for a conventional hospitalization ward supervised by an anaesthesiologist unaware of patient group in the study. Postoperative recordings was assessed on arrival in the ward, at 6, 12, 24, 48 and at 72 hours after the start of surgery. The parameters recorded were: total volume of morphine used from the PCA pump, visual analogy pain score (VAS) 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), and motor power in the operated limb using the modified Bromage scale and ambulation. In addition, at each measuring 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 48 hours. Patients received regular intermittent physiotherapy from day 3 and were encouraged to exercise and walk with assistance as early as possible, pain and motor power allowing. By day 4, patients were encouraged to walk without assistance and to attempt stairs by day 5. Patients' progress was recorded by the physiotherapists, nurses, and medical staff and was assessed for suitability for discharge from day 5.

Before discharge, patients were called up to assess their satisfaction with anaesthetic experience on a ten-point categorical scale (from 0-unsatisfactory to 10-outstanding).

The primary endpoints of the study were the amount of morphine required in the first 24 hours and the comparison of the total amount of morphine used. Secondary endpoints were comparison of VAS score in postoperative 72 h, incidence of side effects (nausea, vomiting and respiratory depression), antiemetic requirements, and patient satisfaction.

Based on prior data, we estimated the standard deviation of 24 h morphine uses to be 12 mg. A sample size of 26 patients per group provides a power of 0.85 for comparing the ITM group with FNB group assuming a mean difference of approximately 10 mg of IV morphine.

Statistical Analysis

Data were expressed as means ± SD, and were analyzed using Student t test or, where applicable, two-way analysis of variance (ANOVA) for repeated measures with time and treatment as the 2 factors. Post hoc comparisons were performed by Bonferroni test. Block difficulty only was expressed as median and interquartile range and analyzed using the Mann-Whitney U test. Statistical analysis and calculation were performed with a personal computer and with Graph Pad statistical software. Statistical significance for all test was a p value <0.05.

Results

Fifty-two patients were accepted for the study. They were allocated to a group before surgery. No complication was recorded during anaesthetic procedures.

Patient characteristics were similar between the 2 groups (Table I), with no statistically significant differences. All the blocks were easily performed, and there were no case of difficulty in-

Table I. Patient characteristics.

Patient characteristics	ITM (n = 26)	FNB (n = 26)	Statistical significance
Age (yrs)	67.4 ± 8.5	68 ± 5.8	$p = 0.1$
Men/women	19/6	14/12	
Weight (kg)	82.1 ± 15.3	75.7 ± 12.9	$p = 0.1$
ASA	1.9 ± 0.7	1.7 ± 0.4	
Height (cm)	163.9 ± 10.3	161.8 ± 8.4	$p = 0.3$
Duration of surgery (min)	123 ± 20	118 ± 23	$p = 0.2$
Time of esecution (min)	6.2 ± 1.5	13.3 ± 2.6	$p = 0.02^*$
Onset time after spinal anestesia (min)	6.6 ± 1.3	6.5 ± 1.6	$p = 0.5$
Block difficulty	2.1	1.4	$p = 0.4$
Patient satisfaction (mm)	9.1 ± 14.03	8.4 ± 14.41	$p = 0.5$

Values are Mean + SD. ITM: Intrathecal Morphine Group. FNB: Femoral Nerve Block Group. No significant differences were found between groups in demographic data. *: $p<0,05$ comparing ITM group and FNB.

dex >3. Time of execution of anaesthesia was obviously higher in FNB group ($p<0,02$). The femoral nerve block was successful in all 26 patients of FNB group.

Eight patients in the FNB and 3 patients in IT group required intra-operative remifentanil (0.1 mcg/kg/min). No patient needed conversion to general anaesthesia. We found no episodes of excessive sedation, respiratory depression or severe hypotension.

VAS values at knee flexion are reported in Figure 1. We found a statistically significant differences between the two groups: ITM group had the lower values from the sixth hour to the full time of observation.

Morphine consumption is shown in Table II. The ITM group had a lower morphine consumption compared to FNB group. However, the difference in the opiate consumption was not statistically different.

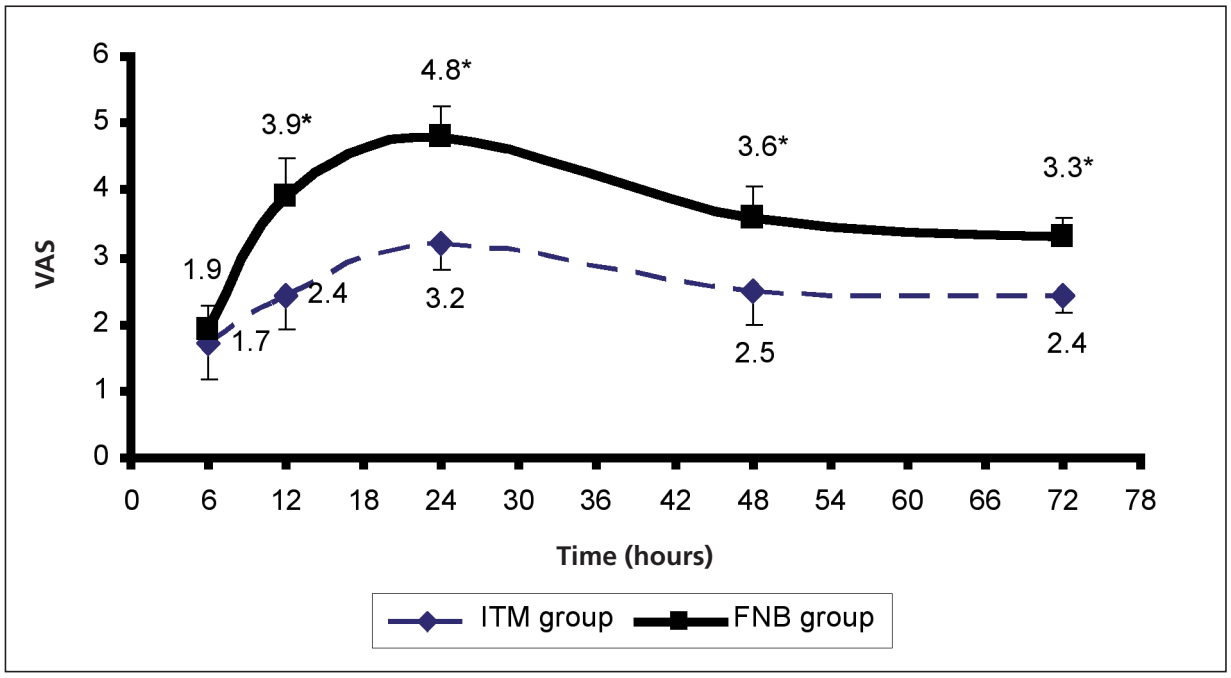

Figure 1. VAS score on knee flexion in the two groups. *p <0,05. Values are Mean (SD). ITM: Intrathecal Morphine Group. FNB: Femoral Nerve Block Group. After 6 h, VAS was lower in ITM group compared with FNB group.

Satisfaction scores were not statistically different (Table I).

The incidence of postoperative side effects was similar: 17 patients in ITM group experienced itching, only 8 in FNB group (Table III). No statistically significant differences were found between the two groups using the Fischer's test. We did not find difference in the two treatment groups in the use of antiemetic and antipruritic medication. No cases of respiratory depression was recorded.

Residual motor blockade in the operated limb (Table IV) in the FNB group was still more pronounced than in the ITM patients (0<0.01 at 6 hr and 12 hr).

Table III. Incidence of side effects.

Patient having	ITM group n = 26	FNB group n = 26	*P* value
Intraoperative discomfort	3 (11%)	8 (31%)	0.1
Nausea and vomiting	9 (35%)	17 (65%)	0.08
Itching	17 (65%)	8 (31%)	0.07
Respiratory depression	0	0	–

Values are number (%). ITM: Intrathecal Morphine Group. FNB: Femoral Nerve Block Group. No statistical differences were found between the two groups.

Discussion

In this randomized, single-blinded, controlled study, our data show that the intrathecal administration of morphine 100 mcg is safe and more effective than single-shot femoral nerve block in order to reduce post-operative VAS after TKA.

Total knee arthroplasty is a major orthopaedic procedure commonly performed in patients with degenerative disease of the knee joint. Despite the beneficial long-term effects, the procedure is associated with intense early post-operative pain, and effective analgesia is mandatory in order to improve the functional recovery and the articular motility[1]. Several reports demonstrated that regional anesthesia is effective to ensure a better post-operative analgesia and reduce neuroendocrine response to the surgical stress, coupled with a lower sensitization of central nervous system and muscle spasm reflex to pain, allowing a rapid mobilization of the knee, and reducing the postoperative hospital stay and the collateral effects of systemic opiates (such as vomiting and nausea)[1,2,8-13].

Femoral nerve block is nowadays recommended for a reduction in pain scores and supplemental analgesia as shown by Fisher et al[6]. Femoral nerve block has been found to facilitate physical therapy and early ambulation, and may reduce the length of hospitalization[1,14]. There are some concerns about continuous perineural infusion of techniques because of heterogeneity in study design and inconsistency of procedure-specific data[6,15]. Another important issue is ultrasound guidance. Marhofer et al[16-17] demonstrated that ultrasound guidance significantly improved the puncture-to-onset interval and the quality of sensory block avoiding complications; moreover less amount of local anaesthetic was required.

Table II. Cumulative morphine use (mg) during the first postoperative 48 hours in intrathecal morphine group compared with femoral nerve block group.

Time (hours)	ITM group n = 26	FNB group n = 26	*P* value
6	0.9 (± 1.7)	3.1 (± 3.4)	0.02
12	4.2 (± 4.3)	6.3 (± 3.0)	0.2
24	6.9 (± 2.1)	10.3 (± 3.0)	0.06
48	9.7 (± 5.1)	13.6 (± 3.1)	0.08

Values are Mean ± SD. ITM: Intrathecal Morphine Group. FNB: Femoral Nerve Block Group. Despite lower amount of morphine PCA in ITM group, no statistical differences were found between the two groups.

Table IV. Motor power in the operated limb.

Time (hours)	ITM group n = 26	FNB group n = 26	*P* value
6	1 (0-3)	3 (0-3)	0.001*
12	0 (0-1)	1 (0-2)	0.01*
24	0 (0)	0 (0-1)	0.08
48	0 (0)	0 (0)	–

Values are median (range). ITM: Intrathecal Morphine Group. FNB: Femoral Nerve Block Group. Modified Bromage scale with 0 grade for no blockade and grade 3 for complete blockade. *p<0,05 comparing ITM group and FNB.

Intrathecal morphine provides effective post-operative pain control for major orthopaedic procedures, and represents an attractive therapeutic option because of its simple administration, which does not expose the patient to an additional procedures[6-7]. Morphine is the recommended opiate in the spinal combination with local anaesthetic basing on procedure-specific evidence in terms of longer duration of analgesic effect respect to lipid-soluble opiates[6]. The major drawback to intrathecal morphine is the frequent incidence of drug-related side effects (sedation, nausea, vomiting, itching, urinary retention, and delayed respiratory depression). Side effects are dose related: previous reports showed the doses necessary for postoperative analgesia in TKA result in a side effect incidence ranging from 50% to 100%[6-7]. Gehling et al[18] concluded the moderate incidence of side-effects seems to be justified by the quality and duration of analgesia provided by low dose intrathecal morphine added to a spinal anaesthesia. Moreover, intrathecal morphine for postoperative analgesia requires measures for prophylaxis and therapy of side-effects and continuous observation of the respiratory function of patients, but patients receiving systemically opiates have the same need[19]. Few reports[20] investigated lower doses of IT morphine for pain relief after TKA. Rathmell et al[7] demonstrated that small dose (100 to 300 mcg) of IT morphine coupled with standard doses of PCA-morphine provides good pain relief after either total hip or total knee arthroplasty. Moreover, the incidence of nausea and vomiting correlated with higher doses of ITM (more than 200 mcg). Murphy et al[21,22] pointed out that 100 mcg of ITM provided the best balance between analgesic efficacy and side effect profile in older patients undergoing hip arthroplasty.

We decided not to block the sciatic nerve because of limited and inconsistent procedure-specific evidences of relevance in treatment of post-operative pain after TKA: there is still no evidence that adding sciatic nerve block is better than a combination of femoral nerve block and systemic analgesia[6,25].

Consensus recommendations for post-operative analgesia following total knee arthroplasty recommend the use of paracetamol in combination or not with other analgesics (NSAIDS and opiates), for its sparing-effect on supplemental analgesic use after orthopaedic procedures[6,23-24]. The use of post-operative systemic strong opiates is recommended in combination with non-opiate analgesia for high-intensity procedure pain. IV PCA is analgesic administration regimen recommended because of its improved pain control and higher patient satisfaction[6].

To our knowledge there are only two studies that have compared femoral nerve block to intrathecal morphine. Tarkkila et al[26] found a better analgesia with 300 mcg of spinal morphine comparing to continuous femoral nerve block, with a similar incidence of side effects. In this study the Authors used a larger dose of morphine; moreover, they did not use an ultrasound guidance to identify the pertinent anatomy of femoral nerve, probably reducing the enhancement in analgesic effectiveness. Finally, patients received oxycodone post-operatively, which could have contributed to a different side effect and analgesic profile[26].

In contrast, Sites et al[27] showed that the two groups of their study achieved equal analgesia, and the femoral block nerve group had significant reduction in opiate-induced side effects, but they used 250 mcg ITM, and their patients did not receive paracetamol in combination with FANS and morphine post-operatively.

Our results show an average VAS lower for the ITM group compared to FNB group for the entire period of observation. The analysis of the VAS trend demonstrated the average VAS in ITM group has been higher after 24h: this finding agrees with the temporal analgesic effect of spinal morphine, which is around 12 and 24 h. In contrast, in FNB group, we found increasing average VAS during the first 12 hours, even if the higher VAS value has been reached after 24 h.

The average PCA morphine consumption have been lower in ITM group; anyway, the difference in the opiate consumption did not reach statistical difference. The p value (0.06) suggest that the sample slightness is the reason of this result.

The incidence of adverse affects has to be point out: we didn't find any event of respiratory depression and, more interesting, any statistical difference in terms of itching, vomiting, nausea and urinary retention between the two groups.

There are two major limitations of our study. First of all, we were not able to measure the success of physical therapy and the time to discharge. This is justified by our institution's predefined clinical pathway. In this clinical pathway, patients remove drainage and start physical therapy 48 hours after surgery. Therefore it's quite difficult to correlate the advantages of analgesic techniques in early mobilization, and also to

compare analgesic efficacy to other reports. Second of all, the sampling was limited: an higher number of patients enrolled could demonstrate that ITM gives a sparing effect on morphine PCA amount, as suggested by our statistical results.

The analysis of the correct use of low dose of spinal morphine in orthopedic surgery requires further studies in order to clarify the effectiveness of the sparing-effect on the consumption of IV morphine in post-operative period, and to analyze the real incidence of adverse effects.

In conclusion, our results show that low dose of intrathecal morphine appears to provide superior analgesia and may be more efficient than femoral nerve block for TKA post-operative analgesia. The low averaging VAS score (maximum VAS score was 5 for FNB group) for the two groups suggest these ways may be both effective in post-operative pain for TKA. On the other and, FNB performed with eco-guidance represents an additional procedure and requires time and specific equipment.

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