Intraoperative single-shot “3-in-1” femoral nerve block with ropivacaine 0.25%, ropivacaine 0.5% or bupivacaine 0.25% provides comparable 48-hr analgesia after unilateral total knee replacement

[Le blocage peropératoire “3 en 1” du nerf fémoral par une dose unique de ropivacaine à 0,25 % ou à 0,5 % ou de bupivacaine à 0,25 % produit une analgésie de 48 h comparable après la mise en place d’une prothèse totale de genou]

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Purpose: To compare analgesia after intraoperative single shot “3-in-1” femoral nerve block (FNB) in combination with general anesthesia using ropivacaine 0.25%, ropivacaine 0.5% with bupivacaine 0.25% for total knee replacement (TKR).

Methods: We performed a randomized, double-blind study in 48 patients for elective TKR under general anesthesia. Patients were randomized to one of four groups (C: sham block, R1: “3-in-1” FNB using 30 mL of ropivacaine 0.25%, R2: “3-in-1” FNB using 30 mL of ropivacaine 0.5%, B: “3-in-1” FNB using 30 mL of bupivacaine 0.25%). Verbal pain score (VPS) both at rest and movement were assessed for 48 hr after TKR (0=none; 1=mild; 2=moderate; 3=severe). Total morphine consumption and its associated side effects, duration of hospitalization after operation were also compared.

Results: There were no differences in patients' physical characteristics, intraoperative morphine usage, operation time, tourniquet time or length of hospitalization between the four groups. When compared with group C, the VPS was significantly lower in groups R1, R2 and B at one, four, eight, 24 and 48 hr after TKR ($P < 0.05$). The morphine requirement of groups R1, R2 and B were also significantly lower when comparing with group C up to 48 hr postoperatively ($P < 0.05$). There were no significant differences in VPS and postoperative morphine requirement at any time between groups R1, R2 and B.

Conclusion: “3-in-1” FNB with ropivacaine provided analgesia that was clinically comparable to that of bupivacaine up to 48 hr after TKR. Increasing the concentration of ropivacaine from 0.25% to 0.5% failed to improve the postoperative analgesia of “3-in-1” FNB.

Objectif : Comparer l'analgésie fournie par l'administration peropératoire d'un bloc “3 en 1” du nerf fémoral (BNF) en une dose unique, combinée à l'anesthésie générale, avec de la ropivacaine à 0,25 %, ou à 0,5 %, ou de la bupivacaine à 0,25 % pour la mise en place d'une prothèse totale de genou (PTG).

Méthode : L'étude randomisée et à double insu comprend 48 patients qui reçoivent une PTG non urgente sous anesthésie générale. On forme quatre groupes (T : groupe témoin avec bloc fictif, R1 : BNF “3 en 1” avec 30 mL de ropivacaine à 0,25 %, R2 : BNF “3 en 1” avec 30 mL de ropivacaine à 0,5 %, B : BNF “3 en 1” avec 30 mL de bupivacaine à 0,25 %). Les scores de l'échelle verbale de douleur (EVD) au repos et pendant le mouvement sont notés pendant 48 h après la PTG (0 = aucune ; 1 = légère ; 2 = modérée ; 3 = sévère). La consommation totale de morphine et ses effets secondaires et la durée de l'hospitalisation postopératoire sont comparés.

Résultats : Les caractéristiques physiques des patients, la consommation de morphine peropératoire, la durée de l'intervention, le temps de garrot ou la durée de l'hospitalisation sont comparables dans les quatre groupes. Comparé à celui du groupe T, le score à l'EVD des groupes R1, R2 et B est significativement plus bas à une, quatre, huit, 24 et 48 h après la PTG ($P < 0,05$). Les besoins de morphine dans les groupes R1, R2 et B sont aussi significativement plus bas que ceux du groupe C jusqu'à 48 h après l'opération ($P < 0,05$). Les scores EVD et la consommation de morphine postopératoire demeurent comparables en tout temps dans les groupes R1, R2 et B.

Conclusion : Le BNF “3 en 1” avec de la ropivacaine fournit une analgésie expérimentale comparable à celle de la bupivacaine jusqu'à 48 h après une PTG. L'augmentation de la concentration de ropiva-

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caine de 0,25 % à 0,5 % ne permet pas d'améliorer l'analgésie postopératoire du BNF "3 en 1".

TOTAL knee replacement (TKR) is an operation commonly performed in the elderly. Pain after TKR is severe and difficult to treat with oral analgesics.^{1,2} Uncontrolled pain results in endocrine, metabolic and inflammatory responses which have adverse effects on various organ functions.³ This is especially detrimental in the elderly cohort with limited physiological reserves.⁴

Ropivacaine, a long-acting amide local anesthetic, has an improved safety profile when compared with bupivacaine. Clinical trials demonstrated less cardiovascular and central nervous system effects when ropivacaine was injected intravenously compared to bupivacaine.^{5–7} Therefore, ropivacaine is advantageous in regional anesthetic techniques requiring large volumes of local anesthetics.

Since its introduction, numerous studies have compared ropivacaine with other available local anesthetics for various regional anesthesia-analgesia techniques.^{8–15} There have been conflicting reports regarding the relative potency of ropivacaine *vs* bupivacaine. Recent publications suggested that there is a difference in the relative potency of the two local anesthetics. This could account for the differences in cardio-toxicity and motor blockade.^{16,17}

The "3-in-1" femoral nerve block (FNB) was first described by Winnie and colleagues in 1973.¹⁸ More recently, Singelyn and colleagues had shown that a *continuous* "3-in-1" FNB using bupivacaine decreased the pain score after TKR and was associated with fewer side effects than continuous epidural analgesia.^{19,20}

Comparison of the clinical efficacy of intraoperative single-shot "3-in-1" FNB using ropivacaine and bupivacaine at lower concentrations for post TKR analgesia has not been conducted. While bupivacaine at 0.25% has been proven effective for post TKR analgesia,^{19,20} the relative therapeutic ratios of the two local anesthetics for lower limb blocks has not been established and the dose of ropivacaine as an alternative for bupivacaine for 3-in-1" FNB is still unclear. In this study, we aimed to compare the postoperative analgesia provided by a single-shot "3-in-1" FNB using either ropivacaine 0.25%, ropivacaine 0.5% or bupivacaine 0.25% in conjunction with general anesthesia after TKR.

Methods

This prospective, randomized, double-blind study was conducted after obtaining Institutional Ethics

Committee approval and written informed consent from patients. Forty-eight ASA I or II patients, scheduled for unilateral TKR, were recruited into our study. Exclusion criteria included age <40 or >80, weight <50 kg or >100 kg, allergy to local anesthetics or acetaminophen, preexisting neurological deficit or inability to understand pain scale or patient-controlled analgesia (PCA) device usage.

During the preoperative visit, patients were briefed on the use of the PCA device and a four-point verbal pain score (VPS). This score was defined as 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain.

Patients were randomly divided into four treatment groups using sealed envelopes:

Group C received a sham block with 30 mL of saline;

Group R1 received "3-in-1" FNB using 30 mL of ropivacaine 0.25% (75 mg);

Group R2 received "3-in-1" FNB using 30 mL of ropivacaine 0.5% (150 mg);

Group B received "3-in-1" FNB using 30 mL of bupivacaine 0.25% (75 mg).

All patients received a standard general anesthesia and the "3-in-1" FNB was performed only at the end of surgery, before emergence from anesthesia. General anesthesia was induced with fentanyl 1.5 $\mu\text{g}\cdot\text{kg}^{-1}$, thiopentone 5 $\text{mg}\cdot\text{kg}^{-1}$ and atracurium 0.5 $\text{mg}\cdot\text{kg}^{-1}$. The trachea was intubated and the ventilation controlled. Anesthesia was maintained with a mixture of isoflurane 1% and nitrous oxide 66% in oxygen. Intraoperative morphine was not restricted and was administered at the discretion of the attending anesthesiologist (not involved in the study). A standard thigh tourniquet inflated to 150 mmHg higher than systolic blood pressure was used on the operated leg for all patients.

During the reversal of anesthesia, "3-in-1" FNB was performed using the landmark described by Winnie and colleagues.¹⁸ This was performed by one of two anesthesiologists (HPN, KFC) with substantial expertise in regional anesthesia who were unaware of the test solution used.

Sterile syringes containing the test solutions were prepared by one of the authors not involved in the nerve block. The femoral artery was palpated below the inguinal ligament and a 10 cm Teflon-coated 22 gauge short-beveled insulated stimulator needle was inserted 1 cm lateral to the pulsations. The femoral nerve was identified with the aid of a nerve stimulator (Stimuplex HNS II, B.Braun, Freiburg, Germany) With an initial output of 2 mA, the needle was advanced at an angle of

TABLE Demographic data, perioperative parameters and duration of stay of the study population

	Group C	Group R1	Group R2	Group B	P value
Age (yr)	65.3 ± 14	64.3 ± 8.6	64.8 ± 5.2	62.8 ± 7.9	NS
Sex (M/F)	3:9	1:11	2:10	1:11	NS
ASA (I/II)	1:11	3:9	1:11	3:9	NS
Weight (kg)	71.3 ± 14.0	65.6 ± 11.4	66.2 ± 8.9	66.4 ± 14.1	NS
Intraoperative morphine (mg)	9.2 ± 3.0	9.6 ± 1.9	9.2 ± 2.3	10.3 ± 0.7	NS
Operation time (minutes)	102.5 ± 21.3	114.6 ± 32.7	98.5 ± 38.0	107.3 ± 28.8	NS
Tourniquet time (minutes)	76.9 ± 16.6	89.3 ± 19.6	80.1 ± 30.5	96.4 ± 32.6	NS
Length of stay (days)	8.8 ± 2.9	9.5 ± 3.4	9.3 ± 3.0	8.8 ± 3.4	NS

Values expressed as mean ± SD or numbers (*n*). NS=not significant; C=sham block; R1="3-in-1" FNB with ropivacaine 0.25%; R2="3-in-1" FNB with ropivacaine 0.5%; B="3-in-1" FNB with bupivacaine 0.25%.

30 to 45° to the skin until quadriceps muscle contractions were elicited. Its position was then optimized and judged adequate when an output of <0.5 mA still elicited contractions of the quadriceps. Test solution was injected after negative aspiration for blood.

Postoperatively all patients received a PCA pump programmed to deliver morphine 1 mg *ip* on demand with a lockout time of five minutes. A continuous background infusion of morphine at 0.01 mg·kg⁻¹·hr⁻¹ was set for the first 24-hr after operation. All patients received oral acetaminophen 1 gram six hourly starting 24 hr after surgery.

Assessment of efficacy was carried out at one, four, eight, 24 and 48 hr postoperatively by an investigator who was blinded to the patient's grouping.

The following four clinical endpoints were assessed in the study: VPS both at rest and movement, cumulative morphine requirement, associated side effects (presence of nausea or vomiting, pruritus, respiratory depression, sedation and injection site infection/hematoma) and duration of hospital stay after TKR.

Respiratory depression was defined as a respiratory rate of less than 8·min⁻¹. Sedation score was defined as 0=awake, 1=drowsy but responsive to verbal stimulus, 2=drowsy but arousable to physical stimulus, 3=unarousable. Physiotherapy only commenced after the study period was over.

A power analysis performed after a pilot study indicated that seven patients were required in each group to detect a clinically relevant difference of 50% reduction in morphine consumption at 48 hr (*P*=0.05, power=0.8).

Statistical analysis was performed with SPSS statistical software (version 10.0; SPSS, Chicago, IL, USA). The Chi-squared test was used for gender, nausea and vomiting score. VPS, and sedation score were analyzed with Kruskal Wallis test. If significant difference

was noted, post hoc Mann-Whitney U test was performed two groups at a time to determine the inter-group differences. Data for age, weight, operation time, tourniquet time, total morphine consumption were analyzed with one-way analysis of variance (ANOVA) followed by a Bonferroni t test correction when appropriate. Data were expressed as mean ± SD or *n*. Significance was determined by a *P* value <0.05.

Results

There were no differences in patients' age, weight, gender, ASA classification, duration of operation, tourniquet time and intraoperative morphine usage between the four groups (Table).

The VPS over 48 hr at rest and during movement are presented in Figures 1 and 2. Except for the VPS at rest at 48 hr after TKR, there were significant differences between the VPS among the four groups at all times both at rest and during movement. At rest, VPS were reduced in groups R1, R2 and B compared to group C at one, four, eight and 24 hr after surgery. During movement, VPS was reduced at all times in groups R1, R2 and B when compared to group C. There were, however, no significant differences in VPS at any time between groups R1, R2 and B.

There were significant differences in cumulative morphine consumption at all times among the four groups. Except for group R1 at four hours after TKR, the amount of morphine consumed was significantly lower when comparing groups R1, R2 and B with group C at all times postoperatively (Figure 3). There was no significant difference in morphine consumption at any time between groups R1, R2 and B.

The incidence of nausea, vomiting, pruritus and sedation were similar among the four groups. No patient had a sedation score of two or more and there was no report of respiratory depression.

FIGURE 1 Verbal pain scores during rest over 48 hr. * $P < 0.05$ compared with group C; ** $P < 0.01$ compared with group C; C=sham block; R1="3-in-1" FNB with ropivacaine 0.25%; R2="3-in-1" FNB with ropivacaine 0.5%; B="3-in-1" FNB with bupivacaine 0.25%.

The length of hospital stay after TKR was similar between the four groups despite better pain relief and less morphine consumption during the first 48-hr after TKR.

Discussion

Our study confirms that pain after TKR is severe. Sixty-six percent of patients in the control group that received only PCA morphine for postoperative analgesia had severe pain on movement up to 48 hr after the operation.

Multi-modal pain therapy (balanced analgesia) is the recommended technique for treatment of postoperative pain.²¹ The rationale for this therapy is to achieve sufficient analgesia due to additive or synergistic effects between different analgesics, with concomitant reduction of side-effects, due to lower doses of analgesics used and differences in their side-effect profiles. Various loco-regional techniques have been employed to reduce postoperative pain after major knee surgery. Epidural or central neural axial block produce superior postoperative analgesia. It is, however, associated with four times

more complications than continuous FNB. These include urinary retention, arterial hypotension and epidural catheter related problems.⁹ Patients scheduled for TKR may also receive prophylaxis against deep vein thrombosis; thus the practice of central neural-axial block is not always possible.

Studies comparing continuous or one-shot "3-in-1" FNB after TKR with epidural and PCA morphine have produced conflicting results.^{19,20,22,23} Hirst and colleagues could not confirm improvements in analgesia provided by single-shot "3-in-1" or continuous FNB for TKR except in the recovery room.²³ However, other investigators have demonstrated decreased pain scores and improvements in early rehabilitation for 48 hr.^{19,20,22}

Innervation of the knee is by the femoral, lateral femoral cutaneous, obturator and sciatic nerves. The relative contribution made by each of the nerves is still unclear. Hugh and colleagues observed equal analgesic efficacy with either femoral or sciatic-FNB. The addition of a sciatic nerve block to the FNB did not provide additional benefits after TKR. They postulat-

FIGURE 2 Verbal pain scores during movement over 48 hr. * $P < 0.05$ compared with group C; ** $P < 0.01$ compared with group C; C=sham block; R1="3-in-1" FNB with ropivacaine 0.25%; R2="3-in-1" FNB with ropivacaine 0.5%; B="3-in-1" FNB with bupivacaine 0.25%.

ed that sciatic innervation of the posterior knee is a relatively minor contribution to postoperative pain after TKR.² However, Hirst and colleagues suggested that the sciatic nerve also provides a major contribution to the innervation of the knee as the reason why FNB is insufficient to significantly reduce morphine requirements or improve analgesia beyond the recovery room in their study.²³

Local anesthetic accumulation and toxicity is a potential problem with continuous "3-in-1" FNB technique compared to single-shot. The performance of continuous "3-in-1" block requires specialized equipment, technical expertise and additional time. The necessity for postoperative monitoring and follow-up add further cost to the performance of continuous "3-in-1" blocks. In our study, we demonstrated that a single-shot "3-in-1" FNB technique using lower concentrations of ropivacaine and bupivacaine decreased pain score and morphine consumption up to 48 hr. This is longer than the expected duration of analgesia of a single-shot "3-in-1" FNB. We postulate that this reduction could be due to the prevention of quadriceps spasm, which is a major contribution to post TKR pain.

Although the pain scores were reduced, they were not optimal, especially during movement. Thirty to 50% of patients in the study groups still experienced moderate pain during movement. As discussed previously, this suggests that the sciatic nerve provides substantial innervation of the knee joint. Addition of other non-steroidal anti-inflammatory drugs as part of balanced analgesia, instead of acetaminophen, may also result in a smaller number of patients with moderate pain.

There were limitations to our study; "3-in-1" FNB was performed under general anesthesia before reversal as we sought to prolong the duration of postoperative analgesia of a single-shot "3-in-1" FNB. There is debate whether FNB should be performed under general anesthesia as there is a greater potential risk of nerve trauma even with the aid of a nerve stimulator. Secondly, we could not study the onset time of the "3-in-1" FNB in the three study groups as it was administered under anesthesia.

In conclusion, our results suggest a "3-in-1" FNB with ropivacaine is as effective as bupivacaine for the relief of pain in the first 48-hr after TKR. As ropiva-

FIGURE 3 Cumulative morphine consumption over 48 hr. * $P < 0.05$ compared with group C; ** $P < 0.01$ compared with group C; C=sham block; R1="3-in-1" FNB with ropivacaine 0.25%; R2="3-in-1" FNB with ropivacaine 0.5%; B="3-in-1" FNB with bupivacaine 0.25%.

caine has a lower potential for systemic toxicity, it may be a more suitable choice of local anesthetic for "3-in-1" FNB. Increasing the concentration of ropivacaine from 0.25% to 0.5% did not significantly improve postoperative analgesia.

Thus, we recommend the use of a "3-in-1" FNB with ropivacaine 0.25% as a component of the multimodal management of postoperative pain in patients undergoing TKR.

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