Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery

[L'administration intrathécale de bupivacaïne avec morphine ou néostigmine comme analgésie postopératoire suivant la mise en place d'une prothèse totale de genou]

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Purpose: To compare the postoperative analgesic efficacy and safety of intrathecal (IT) neostigmine and IT morphine in patients undergoing total knee replacement under spinal anesthesia.

Methods: Sixty patients scheduled for elective total knee replacement under spinal anesthesia were randomly divided into three equal groups which received IT 0.5% hyperbaric bupivacaine 15 mg with either normal saline 0.5 mL, neostigmine 50 μg, or morphine 300 μg. The maximal level of sensory block, duration of analgesia, time to use of rescue analgesics, the overall 24-hr and four-hour interval visual analogue scale (VAS) pain score, and the incidence of adverse effects were recorded for 24 hr after administration.

Results: There was no significant difference in maximal level of sensory block among the three groups. The morphine group had a later onset of postsurgical pain and longer time to first rescue analgesics than the neostigmine group ($P < 0.05$). Overall 24-hr VAS pain scores were significantly higher in the saline group *vs* the morphine and neostigmine groups ($P < 0.05$). Motor block lasted significantly longer in the neostigmine group than in the morphine and saline groups ($P < 0.05$). The incidence of adverse effects was similar in the neostigmine and morphine groups except for pruritus (70%) occurring more frequently in the morphine group than in the neostigmine and saline groups (0%; $P < 0.05$). Overall satisfaction rates were better in the neostigmine group than in the morphine and saline groups ($P < 0.05$).

Conclusions: IT neostigmine 50 μg produced postoperative analgesia lasting about seven hours with fewer side effects and better satisfaction ratings than IT morphine 300 μg.

Objectif : *Comparer l'efficacité et l'innocuité analgésique postopératoire de l'administration intrathécale (IT) de néostigmine et de morphine chez des patients devant subir une arthroplastie totale du genou sous rachianesthésie.*

Méthode : *Soixante patients devant recevoir une prothèse totale de genou sous rachianesthésie ont été répartis au hasard en trois groupes égaux. Ils ont reçu 15 mg de bupivacaïne hyperbare IT à 0,5 % et, soit 0,5 mL de solution salée, soit 50 μg de néostigmine, soit 300 μg de morphine. Le niveau maximal du bloc sensitif, la durée de l'analgésie, l'heure des premières demandes d'analgésiques de secours, les scores de douleur des 24 h d'observation et de chaque intervalle de quatre heures selon l'échelle visuelle analogique (EVA) et l'incidence d'effets indésirables ont été enregistrés pendant 24 h après l'administration médicamenteuse.*

Résultats : *Le niveau maximal de blocage sensitif n'a pas présenté de différence intergroupe significative. Chez les patients avec morphine, la douleur post-chirurgicale s'est installée plus tard et leur première demande d'analgésie de secours a donc eu lieu plus tard que chez les patients avec néostigmine ($P < 0,05$). Les scores de douleur à l'EVA ont été, sur 24 h, significativement plus élevés avec la solution salée vs la morphine ou la néostigmine ($P < 0,05$). La durée du blocage moteur a été significativement plus longue avec la néostigmine qu'avec la morphine ou la solution salée ($P < 0,05$). L'incidence d'effets indésirables a été similaire avec la néostigmine et la morphine, sauf pour le prurit (70 %) qui a été plus fréquent avec la morphine qu'avec la néostigmine ou la solution salée (0 %; $P < 0,05$). Le taux de satisfaction générale a été meilleur avec la néostigmine qu'avec la morphine ou la solution salée ($P < 0,05$).*

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Conclusion : *L'administration IT de 50 g de néostigmine a produit une analgésie postopératoire qui a duré environ sept heures, qui a produit peu d'effets secondaires et de meilleurs taux de satisfaction que 300 g de morphine IT.*

KNEE joint replacement is a major operation leading to significant postoperative pain and associated analgesic requirements, and opioids are commonly chosen for pain relief.[1,2] Intrathecal (IT) and epidural administration of opioids is frequently used to provide postoperative analgesia without sensory or motor blockade. Unfortunately, neuroaxial opioids are associated with adverse side effects, in particular, delayed respiratory depression.[3–5] IT neostigmine produces analgesia in animals and humans, but its side effects, including nausea and vomiting, limit its use in clinical practice.[6–11] Nevertheless, studies have shown that small doses of neostigmine (50 μg) can enhance sensory anesthesia with few side effects when combined with small-dose bupivacaine spinal anesthesia.[6,7] Thus, it is conceivable that the combination of IT 50 μg neostigmine and local anesthetic might improve the quality of spinal anesthesia and prolong postoperative analgesia with few adverse effects. The present study was designed to compare the effects of the addition of IT neostigmine or IT morphine on the characteristics of spinal anesthesia with bupivacaine and to assess their postoperative analgesic efficacy and safety in patients undergoing total knee replacement surgery under spinal anesthesia.

Methods

The protocol was approved by the medical Ethics Committee of our hospital, and written, informed consent was obtained from all patients. Sixty ASA physical status I-III patients scheduled for total knee replacement under spinal anesthesia were included in a prospective, randomized, double-blinded manner. Exclusion criteria included age <40 yr or >80 yr; an ASA physical status greater than III; allergy to local anesthetics; contraindications to spinal anesthesia (coagulation defects, infection at puncture site, preexisting neurological deficits in the lower extremities); a history of opioid dependence; contraindications for nonsteroidal anti-inflammatory drugs (NSAID) (NSAID or aspirin allergy, severe liver disease, or impaired renal function), weight >100 kg.

None of the patients received any pre-medication. IT anesthesia was produced by administering 3 mL of 0.5% (15 mg) hyperbaric bupivacaine (Marcaine®, Astra) in addition to either saline, morphine, or neostigmine (neostigmine methylsulfate 0.5 $mg \cdot mL^{-1}$ vial, Santong Pharmaceutical Co. Ltd., Taiwan) using a 25-gauge Quincke needle in a paramedian approach with patients in the lateral recumbent position. The patients were randomly allocated into three groups of 20. The saline group received normal saline 0.5 mL the morphine group received morphine 300 μg, and the neostigmine group received neostigmine 50 μg.

The anesthesiologist administered 1 mg of midazolam at the minimal interval of five minutes until the patient indicated that appropriate sedation had been achieved. Noninvasive measurements of blood pressure, heart rate (electrocardiogram), oxygen saturation (SpO_2), and respiratory rate continued throughout the anesthesia and the first 24 hr following surgery in the postanesthesia care unit.

All patients were given 500 mL of compound sodium lactate solution as a circulatory preload followed by an infusion of 6–10 $mL \cdot kg^{-1} \cdot hr^{-1}$. Midazolam 1–5 mg was used for intra-operative *iv* sedation. Blood pressure was monitored every three minutes for the first 15 min and every five minutes thereafter. Incremental doses of ephedrine were given to patients whose systolic pressure fell below 100 mmHg. Bradycardia (<50 $beat \cdot min^{-1}$) was treated with *iv* atropine (0.5 mg). Nausea and vomiting were treated with metoclopramide (10 mg) supplemented with *iv* droperidol (1–2.5 mg). Rescue antiemetics were given if vomiting occurred more than once, for nausea lasting more than ten minutes, or at the patient's request. The treatment was repeated if necessary.

The level of sensory block was tested by pin prick and the maximal level of sensory block recorded. The severity of postoperative pain was measured using a 10–cm visual analogue scale (VAS) (0=no pain; 10=the worst possible pain) during rest at four-hour intervals or whenever the patient requested analgesia. Postoperative analgesia was provided with *im* diclofenac 75 mg (Voltaren®, Roche) if the VAS score was four or greater. If necessary, diclofenac administration was repeated 12 hr after the previous injection. The duration of complete analgesia was measured from the time of drug administration to the time when the VAS became greater than zero. The time of administration of the first dose of diclofenac for postoperative pain and the number of diclofenac doses were also recorded. The 24-hr VAS score reflected the patient's assessment of the total pain experienced over the previous 24 hr following IT drug administration. The duration of motor block was recorded from the time of drug administration to the time when patients were able to lift their legs in bed, against gravity. The incidence of adverse effects such as nausea, vomiting,

pruritus, dizziness, and anxiety was evaluated with a 'yes' or 'no' survey. Respiratory depression was defined as a respiratory rate <10 breaths·min^{-1}. All evaluations were performed and recorded at four-hour intervals (except during sleep) over the 24 hr following IT drug administration. Patient satisfaction (yes/no) with postoperative analgesia over the 24 hr was also recorded.

Data were analyzed statistically by analysis of variance with the Kruskal-Wallis test and Fisher's exact test. A P value <0.05 was considered to be statistically significant. Data were expressed as mean ± standard error of the mean (SEM) or mean and the 25–75th percentile confidence interval as appropriate.

Results

Sixty-two patients were included in the study. Two patients in whom general anesthesia was used because of failure of spinal anesthesia were excluded from the study. The three groups of patients in the study did not differ significantly with regard to age, sex, weight, height and duration of surgery (Table I). There was no significant difference in maximal sensory block amongst the three groups of patients. Compared with the saline group, the duration of complete analgesia was significantly prolonged in the neostigmine and morphine groups, and the duration of complete analgesia in the morphine group was prolonged relative to the neostigmine group. The mean time until the first dose of diclofenac was longer for patients in the morphine and neostigmine groups when compared with patients in the saline group, and also prolonged in the morphine group relative to the neostigmine group. There was no difference between groups in the number of *im* diclofenac injections requested in the 24 hr following surgery. The overall 24-hr VAS score was significantly higher for patients in the saline group than in patients in the morphine and neostigmine groups (Table II). The VAS pain score was significantly lower in the morphine group at eight hours, after which no significant difference was noted among the three groups (Figure). Motor block lasted significantly longer in the neostigmine group than in the morphine and saline groups (Table II). Adverse effects observed in the study and satisfaction rates are shown in Table III. No significant differences in the incidence of dizziness or anxiety were observed. The frequency and severity of nausea and vomiting were significantly increased in the neostigmine group compared with the saline group, but similar between the neostigmine and morphine groups. Pruritus occurred more frequently in the morphine group than in the neostigmine and saline groups. The overall satisfaction rate was significantly higher in the neostigmine group than in the morphine and saline groups. No respiratory depression was observed in the three groups.

TABLE I Demographic data

	Saline	*Morphine*	*Neostigmine*	
Age (yr)	65 ± 6	62 ± 8	63 ± 9	NS
Sex (M/F)	8/12	10/10	9/11	NS
Weight (kg)	68.3 ± 5.2	66.5 ± 7.2	67.7 ± 8.5	NS
Height (cm)	165.1 ± 8.8	164.5 ± 6.9	165.2 ± 9.7	NS
Surgery duration (min)	122 ± 19	127 ± 18	129 ± 14	NS

Values are expresses as mean ± SEM.
NS=non significant.

TABLE II Spinal anesthesia characteristics and postoperative data

Group	*Saline*	*Morphine*	*Neostigmine*	
Number of patients	20	20	20	
Maximal level of sensory block	T 3.5 ± 0.3	T 3.8 ± 0.2	T 3.6 ± 0.3	NS
Duration of absolute analgesia (min)	320.7 ± 24.6	615.3 ± 64.7†	443.2 ± 35.4*	
First diclofenac (hr)	6.1 ± 1.2	12.5 ± 2.6†	9.3 ± 2.2*	
Number of *im* 75 mg diclofenac injections	2 (1–2)	2 (0–2)	2 (1–2)	NS
24-hr VAS assessment	3.6 ± 0.9	1.6 ± 0.5*	2.2 ± 0.7*	
Duration of motor block (hr)	4.7 ± 0.3	4.5 ± 0.2	5.7 ± 0.4*	

Number of 75 mg diclofenac *im* injections are expressed as means (25–75%). Other data are expressed as means ± SEM. * P <0.05 compared with saline group. † P <0.05 compared to the other two groups. Absolute analgesia= the time of neostigmine administration to the time when the visual analog score (VAS) pain score became greater than zero. NS=non significant.

TABLE III Incidence of side effects and satisfaction rate

	Saline	*Morphine*	*Neostigmine*	
Nausea/vomiting	1/20	5/20	7/20*	
Pruritus	0/20	14/20†	0/20	
Dizziness	0/20	5/20	4/20	NS
Anxiety	0/20	0/20	3/20	NS
Respiratory depression	0/20	0/20	0/20	NS
Satisfaction	1/20	4/20	11/20†	

NS=non significant. * P <0.05 compared with the saline group. † P <0.05 compared to the other two groups.

Discussion

There is little comparative data showing how postoperative analgesic effects differ between neostigmine and conventional IT opioids. The purpose of this

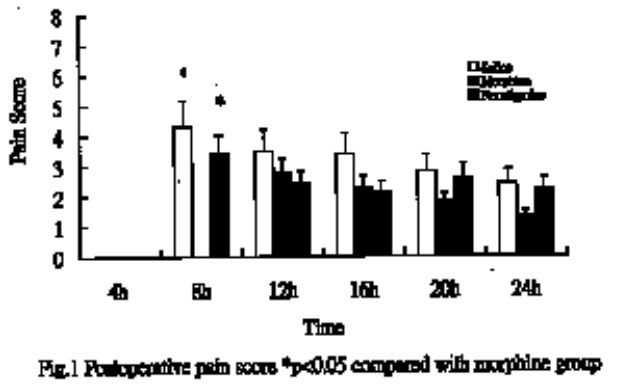

Fig.1 Postoperative pain score *p<0.05 compared with morphine group

FIGURE

study was to compare the analgesic effects of IT neostigmine and IT morphine using analgesic demand and VAS pain scores. Preliminary dose-response studies in volunteers and patients undergoing surgery showed that IT neostigmine provided analgesia when given at doses 10 μg for surgical patients, at doses 50 μg for volunteers, and induced few side effects at doses 50 μg.[6–10] For the purpose of this study, the dose was chosen to maximise the analgesic efficacy whilst minimizing the potential side effects of neostigmine in view of the route of administration and to limit the extent of side effects. The 50 μg dose of neostigmine in this age group was therefore chosen to minimize perioperative side effects, in particular, nausea and vomiting. Spinal cord toxicity resulting from IT neostigmine has not been reported.[12–14]

We found that IT neostigmine prolonged the effect of spinal anesthesia, in terms of both the duration of complete analgesia and the time until postoperative analgesic was first requested, relative to the saline group. Compared with the morphine group, the duration of complete analgesia and the time until the first request for analgesic in the neostigmine group were shorter. When analgesic was first requested in the three groups after surgery, patients made one or two requests for doses of diclofenac to achieve adequate analgesia. Since the overall 24-hr VAS pain scores were significantly higher in the saline group relative to the neostigmine and morphine groups, it would seem that there was some residual analgesic effect in the morphine and neostigmine groups over that period. Effective postoperative pain relief over the 24 hr following total hip surgery has been reported with 0.1 mg IT morphine doses.[15] However, motor blockade may also help explain the residual analgesia found in the neostigmine group. After open knee surgery, pain can be associated with severe reflex spasms of the quadriceps muscle, causing further pain and impaired muscle function. The addition of 50 μg neostigmine prolongs motor blockade at the quadriceps from bupivacaine spinal anesthesia via an acetylcholine (Ach)-mediated reduction in motor neuron outflow.[7] In addition to the direct inhibition of motor activity resulting from the administration of neostigmine, increased spinal levels of Ach may augment motor blockade as a result of the axonal conduction block caused by spinal bupivacaine.[10] Neostigmine-enhanced motor block after spinal administration of local anesthetics can be a troublesome side effect postoperatively but may be useful in surgery requiring muscle relaxation, such as total knee replacement surgery. Confirmation of this hypothesis warrants specific investigation.

IT morphine is considered to be the "preferred" route of neuroaxial opioid administration owing to the ease of the technique, the simplicity of postoperative management, and the immediate availability of opioid in the cerebrospinal fluid for binding to dorsal horn receptors.[5] The major concern in IT morphine administration is respiratory depression. Previous studies[3] have recommended doses of 0.4–0.5 mg for hip and knee surgery. Small or "mini-dose" morphine (< 1.0 mg) has been reported as being effective for the management of acute postoperative pain after a variety of surgical procedures, producing no signs of respiratory depression.[3] Few problems with respiratory depression occur with IT morphine doses around 0.3–0.5 mg,[16] therefore dosages of this order may represent the safest compromise when choosing an IT morphine dose. For these reasons, we chose a relatively low dose of 0.3 mg morphine for this study, and respiratory depression, defined as a respiratory rate 10 min^{-1} , was not noted in any of the patients enrolled in the study. Defining optimal IT morphine doses requires complex balancing of risks and benefits. Patient age, medical condition, and pain intensity are likely to be important factors.[17] It is possible that healthy patients undergoing extensive and more painful procedures such as total knee surgery may be less susceptible to IT morphine-induced respiratory depression. IT neostigmine has been shown to have a discernible stimulatory respiratory effect.[7]

How the analgesic effect of IT neostigmine relates to the nature of the surgery, the type of pain, or both is yet to be determined. Previous studies[8,9,18] have shown that IT neostigmine provided analgesia at doses 10 μg for patients undergoing Cesarean section, vaginoplasty, and below knee orthopedic surgery. In

contrast, 100 μg of IT neostigmine was unable to provide adequate analgesia for patients undergoing more painful surgery such as abdominal hysterectomy.[19] From these studies, it seems that the dose-dependency of IT neostigmine-induced postoperative analgesia depends on the nature of the noxious stimuli, the type of anesthesia used, the methods of analgesic administration and the assessment of analgesic effect. To our knowledge, this is the first study to evaluate the analgesic effects of IT neostigmine after total knee replacement surgery. The study showed that IT neostigmine can provide effective analgesia in more painful procedures such as total knee replacement surgery.

Nausea and vomiting, the most common and troublesome side effects of IT neostigmine, restrict its clinical use. IT neostigmine has been shown in clinical studies to produce nausea and vomiting in a dose-related manner.[7,9,18] The incidence of nausea and vomiting induced by IT neostigmine was similar to that seen in our previous study.[20] In accordance with the findings of our previous research,[20] both droperidol and metoclopramide were ineffective in stopping vomiting. Nausea and vomiting resolved with time when the effects of the spinal neostigmine abated. IT morphine also induced nausea and vomiting, and there were no significant differences between the IT neostigmine and IT morphine groups in the incidence of nausea and vomiting.

Pruritus occurred more frequently in the IT morphine group. Since most of the patients receiving IT morphine cited side effects including pruritus as reasons for dissatisfaction, the high incidence of pruritus was clearly troublesome. Pruritus is the most common side effect of IT opioid administration and is typically localized to the face, neck, or upper thorax and usually occurs within a few hours of administration.[21] Pruritus induced by IT opioid administration is believed to be due to cephalad migration of the drug in cerebrospinal fluid and subsequent interaction with opioid receptors in the central nervous system, but its mechanism remains unclear. Opioids can liberate histamine from mast cells, but this does not appear to be the mechanism underlying the pruritus following IT morphine administration. Nevertheless, anti-histamines can be an effective treatment for such pruritus, probably because of their sedative effects, and are widely used for this indication.[22] *I V* diphenhydramine was used for symptomatic pruritus and was generally ineffective in diminishing pruritic symptoms. Six patients failed to respond to diphenhydramine, and the others gained little symptomatic relief.

In conclusion, in patients undergoing total knee replacement surgery under spinal anesthesia, IT 300 μg morphine produced longer lasting analgesia with a duration of about ten hours compared to IT 50 μg neostigmine which resulted in postoperative analgesia lasting about seven hours. Both neostigmine and morphine provided longer postoperative analgesia than placebo. The incidence of adverse effects was similar for the neostigmine and morphine groups, except for pruritus, which occurred more frequently in the morphine group. The patient assessed rate of analgesic satisfaction was higher in the neostigmine group than in the morphine and normal saline groups.

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