THE EFFICACY OF SMALL DOSE OF INTRATHECAL NEOSTIGMINE IN MODULATION OF POSTOPERATIVE ANALGESIA AFTER ORTHOPEDIC SURGERY

By

Ayman S.H. Rofaeel, MD, Mohamed A. Sultan, MD, Amer A. Attia, MD

From

The Department of Anesthesia and Surgical Intensive Care, Faculty of Medicine, Mansoura University, Egypt.

ABSTRACT

Background : This prospective randomized study was designed to compare the analgesic efficacy and safety of intrathecal (IT) neostigmine, IT morphine, versus IT bupivacaine in patients undergoing lower extremity orthopedic surgery. *Methods :* The study included sixty patients, 25 to 50 years old, ASA I and II, who were scheduled for lower extremity orthopedic surgery. According to the regimen used for subarachnoid block, patients were randomly assigned to one of three equal groups. The control group received 12.5 mg 0.5% bupivacaine. The other groups received either 100 µg morphine (morphine group) or 25 µg neostigmine (neostigmine group), combined with 12.5 mg 0.5% bupivacaine. The onset of sensory and motor blockade, duration of analgesia, and the incidence of postoperative pain were recorded. The adequacy of postoperative analgesia was assessed using pain score. Patients were also observed for adverse effects such as hypotension, bradycardia, nausea and vomiting, pruritus, respiratory depression, dizziness, and headache. *Results :* The onset of sensory and motor blockade did not differ significantly among the three groups. Compared with the control group, both the morphine and neostigmine groups were similarly associated with significant prolongation of the duration of analgesia ($P < 0.01$), and significant reduction of both the incidence and degree (score) of postoperative pain ($P < 0.05$). Among the studied groups, the incidence of

nausea and vomiting was similar, but pruritus was significantly more common in the morphine group ($P < 0.05$). No other adverse effects were detected. *Conclusion :* When combined with bupivacaine spinal anesthesia for orthopedic surgery, the analgesic efficacy of IT neostigmine (25 μg) was similar to that of IT morphine (100 μg), and better than bupivacaine alone. Pruritus was only observed with IT morphine.

Keywords; Intrathecal neostigmine; intrathecal morphine; postoperative analgesia

INTRODUCTION

Poor quality of postoperative analgesia is associated with many adverse hemodynamic, respiratory, metabolic, and hemostatic alterations that negatively influence the surgical outcome[1,3]. Spinally mediated analgesia can be achieved by several mechanisms. Nonspecific axonal blockade is achieved by local anesthetics, whereas specific blockade of nociception may be accomplished by direct agonists which stimulate specific receptors in the spinal cord, such as opioids and alpha-2 adrenergic agonists[4]. Despite the widespread administration of neuraxial morphine for management of acute and chronic pain, its side effects such as nausea, vomiting, pruritus, and respiratory depression still represent a major concern[5].

Intrathecal (IT) neostigmine, unlike direct agonists, was reported to produce analgesia through inhibition of the breakdown of spinally released acetylcholine in the dorsal horn[6] and spinal meninges[7]. In the spinal cord, acetylcholine-induced analgesia is mediated through a direct action on muscarinic[8] and nicotinic receptors[9], and indirectly through stimulation of the release of nitric oxide[10].

Despite the advances in management of postoperative pain, an optimal analgesic regimen balancing superior antinociceptive efficacy with minimal side effects may be difficult to achieve. In this study, we hypothesized that IT neostigmine, through its dual mechanisms of action on the cholinergic and nitric oxide pathways, may represent a novel approach in achieving optimal postoperative analgesia. The use of a small dose of IT neostigmine (25 μg) may also serve to minimize adverse effects. The aim of this prospective study was to evaluate the postoperative analgesic effica-

cy and safety of IT morphine, IT neostigmine as part of analgesic regimen with IT bupivacaine, versus IT bupivacaine alone in candidates for lower extremity orthopedic surgery.

PATIENTS AND METHODS

This study included sixty patients of either sex, 25 to 50 years old, and ASA physical status I or II, who were submitted for operative stabilization of femoral fractures at the Emergency Hospital, Mansoura University. The study was approved by the local ethics and research committee, and an informed consent was secured from all patients. The exclusion criteria included the presence of contraindication(s) to spinal anesthesia (e.g., coagulation defects, neurological deficits in the lower extremities, or infection at the puncture site), or known allergy to any of the test drugs. Multiple traumatized or hemodynamically unstable patients w ere also excluded from the study. Preoperative assessment included history, physical examination, and routinely performed laboratory investigations (e.g., complete blood count, coagulation profile, fasting blood glucose, serum creatinine, and liver function tests).

Intravenous (i.v.) line was established using 18-20 Gauge i.v. catheter, and all patients received 10 ml/kg of normal saline (0.9%) solution as circulatory preload over 1 hour before spinal anesthesia. Intraoperatively, i.v. infusion of normal saline was maintained at 6-8 ml/kg/hour. Any blood loss less than 500 ml was further replaced by normal saline giving triple the volume of blood loss, while whole blood was used for replacement if blood loss exceeded 500 ml.

Patients were randomized according to sealed envelope assignment to three equal groups (20 patients each); the control group received 12.5 mg bupivacaine, the morphine group received 100 µg morphine plus 12.5 mg bupivacaine, whereas the neostigmine group received 25 µg neostigmine plus 12.5 mg bupivacaine.

In the control group, 2.5 ml of 0.5% hyperbaric bupivacaine (equal to 12.5 mg) was diluted using dextrose 5% (D5W) to 3 ml volume. Morphine (10 mg/1 ml) was diluted to 10 ml using D5W (1 ml = 1 mg), then 1 ml of the diluted solution was further diluted to 5 ml (0.5 ml = 100 ug). Neostigmine methylsulfate (0.5 mg/1 ml) was diluted to 10 ml using D5W (0.5 ml = 25 ug). In the morphine and

neostigimine groups, 0.5 ml of the final diluted solution of test drug was mixed with 2.5 ml bupivacaine in the same syringe. The total volume of spinal injectate reached 3 ml in all groups. After proper sterilization and local infiltration anesthesia (1 ml of 1% lidocaine) of the skin over the selected lumbar interspace, subarachnoid block was performed using 25 Gauge spinal needle through a midline approach at the L3-4 interspace in the sitting position. Once free flow of clear cerebrospinal fluid was obtained, the test drugs were injected slowly over 30 seconds. The patient was immediately placed in the supine position with elevation of the head 30 degrees and he was maintained in the same position throughout surgery. Supplemental oxygen was delivered through a face mask at a rate of 5 L/min during surgery. The onset of sensory block was determined by loss of sensation to pinprick below the 10^{th} thoracic dermatome. The onset of complete motor block was assesed by Bromage scale; 0 = no paralysis, 1 = unable to raise the extended leg, but flexes the knee, 2 = unable to flex the knee but flexes the foot, 3 = complete block; unable to move the foot. Intraoperative sedation was achieved by i.v. midazolam (2-3 mg). Electrocardiogram (ECG), heart rate (HR), noninvasive blood pressure, oxygen saturation (SpO_2), and respiratory rate (RR) were continuously monitored throughout the study period. Vital parameters [HR, mean arterial blood pressure (MAP), SpO_2, and RR] were recorded at 1 hour preoperatively (basal values), at 5, 10, and 15 minutes after intrathecal injection, and then every 15 minutes till the end of surgery. Intraoperatively, hemodynamic management included increasing the rate of fluid infusion and/or administration of incremental doses of i.v. ephedrine (5 mg) for hypotension (decrease in the MAP > 20% below the basal value), and incremental doses of i.v. atropine (0.2 mg) for bradycardia (HR < 60 beats/min).

Arterial carbon dioxide tension ($PaCO_2$) and arterial oxygen tension (PaO_2) were checked through arterial blood gas measurement, which was performed initially at 1 hour preoperatively, and 1 hour intraoperatively. It was then repeated if a decrease in respiratory rate (< 10 breaths/min) and/or SpO_2 (< 90%) was recorded at any time during follow up. Postoperatively, vital parameters were recorded and pain score was assessed at intervals of 1,2,3,6,12,18, and 24 hours.

The degree of postoperative pain was scored as: no pain = 0, very mild = 1, mild = 2, moderate = 3, severe = 4, and intolerable = 5 (11). The duration of analgesia was recorded as the time from the onset of sensory blockade till the patient's first request for rescue analgesia, which was provided by nonsteriodal anti-inflammatory drugs (intramuscular diclofenac 75 mg). Throughout the study period, the incidence of adverse effects such as nausea, vomiting, pruritus, respiratory depression (respiratory rate < 10 breaths/min), dizziness, and headache was recorded. Vomiting was treated with i.v. metoclopramide (10 mg), whereas pruritus was treated with i.v. nalbuphine (3 mg).

Statistical Analysis :

Data were analyzed using Statistical Package for Social Science (SPSS, version 9), and were expressed as mean±SD, median (range), or frequency (%) as appropriate. Continuously distributed values were analyzed using one way ANOVA (for comparison between mean values of the three groups) or repeated measure ANOVA (for intragroup comparison), followed by Bonferroni correction if significance was detected. Kruskal-Wallis test was used to analyze differences in pain score among the studied groups, while the incidence of adverse effects was analyzed using Fisher's exact test. A probability (P) value <0.05 was considered to be statistically significant.

RESULTS

The patients' characteristics, duration of surgery, and the onset of sensory and motor blockade did not differ significantly among the studied groups (tables 1 & 2).

Intraoperatively, HR decreased significantly from the basal value at 10 and 15 minutes in the control and morphine groups, and at 10 minutes in the neostigmine group (P <0.05; figure 1). Similarly, MAP decreased significantly from the basal value at 5, 10, and 30 minutes in the control group, at 15 and 30 minutes in the morphine group, and at 10 minutes in the neostigmine group (P <0.05; figure 2). However, neither a decrease in HR below 60 beats/min nor a decrease in MAP more than 20% from the basal value was encountered allover the monitoring period (table 5).

Throughout the study period, recordings of RR, SpO_2, $PaCO_2$ and PaO_2 remained within their physiologic limits in all groups.

The duration of analgesia was significantly longer in both the morphine and neostigmine groups (12.1 ± 1.7 and 11.8 ± 2.1 hours respectively) as compared with the control group (4.6 ± 0.7 hours) ($P < 0.01$; table 2). The incidence of postoperative pain was significantly higher in the control group than in the morphine and neostigmine groups till 18 hours postoperatively ($P < 0.05$; table 3). All patients in both the morphine and the neostigmine groups were pain-free up to 6 hours postoperatively, when only one patient out of each group started to suffer very mild pain (pain score of 1). The incidence of postoperative pain then increased progressively over the subsequent follow up intervals till 24 hours postoperatively, when no significant difference among the three studied groups could be detected. Moreover, there was a significant reduction in pain score in both the morphine and neostigmine groups as compared with the control group from 1 hour till 18 hours postoperatively ($P < 0.05$; table 4). At 24 hours postoperatively, pain scores did not differ significantly among the three groups. Throughout the postoperative period, both the morphine and neostigmine groups did not differ significantly as regards either the pain score or the incidence of pain.

The incidence of nausea and vomiting did not differ significantly among the studied groups. However, the incidence of pruritus was significantly higher in the morphine group than in the other groups ($P < 0.05$). Respiratory depression, dizziness, or headache was not observed in any of the studied groups (table 5).

Table 1. Patients characteristics and duration of surgery in the studied groups.

	Control group (n = 20)	Morphine group (n = 20)	Neostigmine group (n = 20)
Age (years)	35.8 ± 8.9	36.1 ± 9.5	35.4 ± 7.9
Gender (m/f)	13/7	11/9	10/10
Weight (kg)	75.6 ± 5.9	74.1 ± 7	73.5 ± 8.1
Height (cm)	170.7 ± 7.5	171.8 ± 14	172.8 ± 10
Duration of surgery (min)	119.3 ± 23.2	120.8 ± 22.5	114.8 ± 22.9

Values are expressed as mean ± SD.

Table 2. Characteristics of spinal anesthesia in the studied groups.

	Control group (n = 20)	Morphine group (n = 20)	Neostigmine group (n = 20)
Onset of sensory block (min)	4.1 ± 0.3	3.8 ± 0.3	4 ± 0.2
Onset of motor block (min)	5 ± 0.4	4.9 ± 0.5	5.2 ± 0.2
Duration of analgesia (hours)	4.6 ± 0.7	12.1 ± 1.7 *	11.8 ± 2.1 *
Range	(3.6 - 5.4)	(10.2 - 14.8)	(9.5 - 14.3)

Values are expressed as mean ± SD.
* Significant difference in both the morphine and neostigmine groups in comparison with the control group (P <0.01).

Table 3. The incidence of postoperative pain in the studied groups.

Postoperative time	Control group (n = 20)	Morphine group (n = 20)	Neostigmine group (n = 20)
1 h	17 (85%) *	0 (0%)	0 (0%)
2 h	20 (100%) *	0 (0%)	0 (0%)
3 h	20 (100%) *	0 (0%)	0 (0%)
6 h	20 (100%) *	1 (5%)	1 (5%)
12 h	20 (100%) *	12 (60%)	11 (55%)
18 h	20 (100%) *	14 (70%)	15 (75%)
24 h	20 (100%)	19 (95%)	20 (100%)

Values are expressed as number and percentage (%).
* Significant difference in the control group in comparison with both the morphine and neostigmine groups (P <0.05).

Table 4. Postoperative pain score in the studied groups.

Postoperative time	Control group (n = 20)	Morphine group (n = 20)	Neostigmine group (n = 20)
1 h	2 (0 – 2)	0 (0 – 0) *	0 (0 – 0) *
2 h	2 (1 – 4)	0 (0 – 0) *	0 (0 – 0) *
3 h	3 (2 – 4)	0 (0 – 0) *	0 (0 – 0) *
6 h	4 (3 – 4)	0 (0 – 1) *	0 (0 – 1) *
12 h	4 (4 – 4)	1 (0 – 2) *	1 (0 – 3) *
18 h	4 (4 – 4)	2 (0 – 2) *	2 (1 – 3) *
24 h	4 (4 – 4)	3 (0 – 3)	3 (1 – 3)

Values are expressed as median (range).
* Significant difference in both the morphine and neostigmine groups in comparison with the control group (P <0.05).

Table 5. The incidence of adverse effects in the studied groups.

	Control group (n = 20)	Morphine group (n = 20)	Neostigmine group (n = 20)
Nausea and vomiting	1 (5 %)	2 (10 %)	2 (10 %)
Pruritus	0 (0%)	4 (20 %) *	0 (0%)
Bradycardia ¶	0 (0%)	0 (0%)	0 (0%)
Hypotension §	0 (0%)	0 (0%)	0 (0%)
Respiratory depression	0 (0%)	0 (0%)	0 (0%)
Dizziness	0 (0%)	0 (0%)	0 (0%)
Headache	0 (0%)	0 (0%)	0 (0%)

Values are expressed as number and percentage (%).
¶ Bradycardia; heart rate < 60 beats/min.
§ Hypotension; decrease in MAP > 20% of its basal value.
* Significant difference in the morphine group as compared with the other groups (P < 0.05).

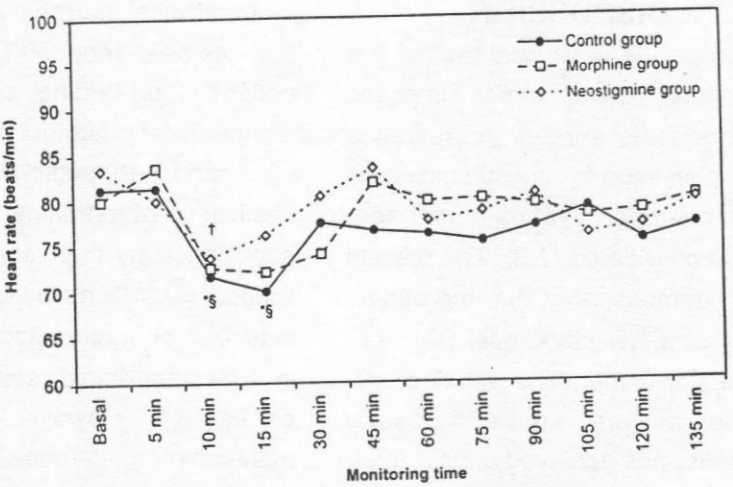

Figure 1. Intraoperative changes in heart rate
Basal value; 1 hour preoperatively
Significant difference from the basal value in the control*, morphine§, and neostigmine+ groups (P<0.05).

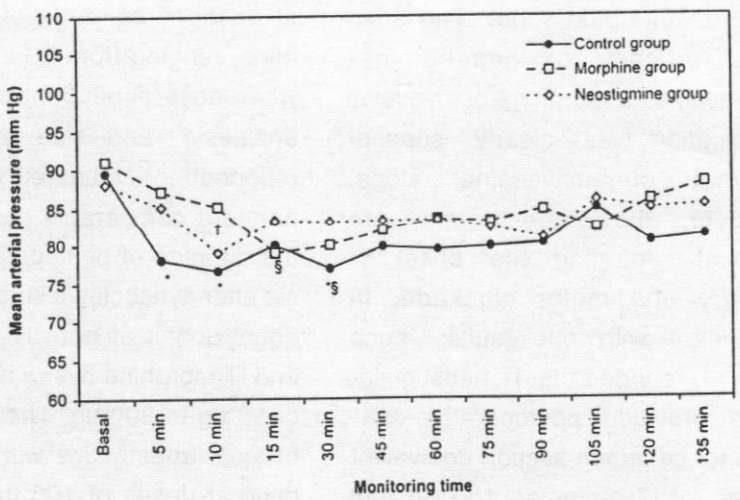

Figure 2. Intraoperative changes in mean arterial blood pressure
Basal value; 1 hour preoperatively
Significant difference from the basal value in the control*, morphine§, and neostigmine+ groups (P<0.05).

DISCUSSION

The extensive surgical trauma and the overwhelming stress imposed by orthopedic surgery represent a major challenge for anesthesiologists when postoperative pain management is considered (1-3). The present study demonstrated that the combination of either intrathecal (IT) neostigmine or IT morphine with IT bupivacaine at the studied dosage regimens, has achieved similar analgesic efficacy. This was evident through a comparable prolongation of the duration of analgesia, and reduction of both the incidence of postoperative pain and degree of postoperative pain score. The analgesic efficacy of neostigmine-bupivacaine or morphine-bupivacaine combination was clearly superior to that of bupivacaine alone. However, the three groups were identical regarding the onset of sensory and motor blockade. In agreement with our results, Chung et al[12], reported that IT neostigmine 25 μg provided postoperative analgesia for cesarean section equivalent to that of IT morphine 100 μg, but neither IT morphine nor IT neostigmine was shown to fasten the onset of sensory and motor blockade from bupivacaine anesthesia[12,13].

Intrathecal morphine administration has been reported to provide excellent, long-lasting postoperative analgesia for obstetric[14,15], urologic[16] and orthopedic procedures[5]. Facilitation of morphine-induced antinociception by bupivacaine was described[17], which may result from the induction of conformational changes in the spinal opioid receptors by bupivacaine[18]. However, the use of intrathecal morphine may be limited by a frequent incidence of side effects, especially delayed respiratory depression and pruritus[19].

Previous studies have used several dosage regimens of IT neostigmine, ranging from 50 μg to 750 μg, when dose dependant postoperative analgesia and side effects were reported[20,21]. Lauretti et al[22], reported a comparable prolongation of the duration of postoperative analgesia after gynecologic surgery between equal doses of both IT neostigmine and IT morphine over a dosage range of 50 ug to 200 ug. The combination of local anesthetics with IT neostigmine at doses of 100 μg[23] and 50 μg[24] was reported to prolong the duration of sensory and motor blockade, and to provide longer duration of analgesia, although increased the inci-

dence of side effects.

However, high doses of IT neostigmine (> 100 μg) were reported to produce many adverse effects such as an increase in blood pressure and heart rate, severe nausea and vomiting, motor weakness, sedation, and reduction in deep tendon reflexes[20].

Based on the dosage scale previously investigated for both IT morphine and IT neostigmine, relatively small doses of both drugs (100 μg and 25 μg respectively) were selected in this study, in order to improve their safety profile.

The enhanced analgesic efficacy of neostigmine in postoperative setting was proposed to result from greater release of spinal acetylcholine from the intense and more prolonged discomfort of postoperative pain, which activates a preexistant spinal cholinergic tonus. Furthermore, acetylcholine preserved after IT neostigmine administration will lead to an increased total concentration of acetylcholine in the cerebrospinal fluid (CSF), and an improved bioavailability at muscarinic and nicotinic nerve terminals in the spinal cord (13). Pharmacokinetic studies demonstrated that CSF neostigmine concentrations, even after the lowest doses of spinal neostigmine, were adequate to significantly inhibit cholinestrase in CSF, allowing sustained plateau of increased acetylcholine concentration in CSF, and thus produce analgesia in the lower extremities[25].

Further analgesic effect of IT neostigmine involves stimulation of the synthesis of nitric oxide in the dorsal horn neurons that contain choline acetyltransferase [26,27], and in the intermediolateral cell column regions of the spinal cord where muscarinic receptors have been identified [28,29]. Lauretti et al[13], suggested that nitric oxide and IT neostigmine enhances each other's antinociceptive effects.

The augmentation of spinal bupivacaine with a small dose of neostigmine may be benificial in the surgical settings because IT neostigmine may have greater analgesic effects in that situation[24]. It is also speculated that the increased spinal levels of acetylcholine may augment motor blockade from spinal bupivacaine. Since IT neostigmine was reported to prolong the duration of motor blockade, it could be argued

that such effect might limit its clinical usefulness in outpatient spinal anesthesia[23,24]. Nevertheless, neostigmine-enhanced motor blockade may be useful in some clinical settings, such as lower extremity surgical procedures which require profound muscle relaxation that may not be achievable with IT bupivacaine alone [24,30]. Since lower extremity orthopedic procedures are usually performed as inpatient procedures, and as IT neostigmine is more efficient for relief of somatic rather than visceral pain [31], the combination of IT neostigmine with IT bupivacaine seems to provide satisfactory analgesia after orthopedic surgery.

In the present study, few recordings of statistically significant decrease in heart rate (HR) and mean arterial pressure (MAP) from basal values were encountered intraoperatively in the three groups. However, these recordings were considered to be clinically irrelevant, since they still remained within the physiologic limits of both HR and MAP. Furthermore, the predetermined levels of bradycardia or hypotension that mandate intervention were not encountered throughout the monitoring period.

The functional sympathectomy induced by IT bupivacaine represents a major precipitating factor for hypotension [32]. Following IT morphine administration, hypotension may not be uncommon, and is probably attributed to the existence of opioid receptors on the preganglionic sympathetic nerves, the blockade of which can reduce the sympathetic activity [33]. Neverthless, neostigmine was reported to increase the activity of preganglionic sympathetic neurons in the spinal cord, and to counteract the sympatholytic effects of spinal anesthesia [20]. However, this cardiovascular stimulatory effect is evident only with large doses of IT neostigmine (>150 μg) (20,24). Moreover, it was reported that small doses of IT neostigmine (<100 μg) may not even prevent local anesthetic-induced hypotension (34-36).

In agreement with these reports, the use of much smaller dose of neostigmine (25 μg) in our study probably explains the lack of the stimulatory effect of neostigmine on hemodynamics during spinal anesthesia.

In the studied groups, no evidence of respiratory depression was detected, as indicated by the virtually un-

changed levels of respiratory rate, oxygen saturation, arterial carbon dioxide tension, and arterial oxygen tension from preoperative values. In accordance with our study, previous studies found no respiratory depressant effect with doses of IT morphine < 200 µg [37] or with IT neostigmine [12]. Nevertheless, IT neostigmine may have a respiratory stimulant effect due to stimulation of the pontine centers of respiratory control from cephalad distribution [38]

In this study, the incidence of nausea and vomiting did not differ significantly among the studied groups, which may be attributed to the use of small doses of IT morphine and neostigmine (100 µg and 25 µg respectively). In contrast with our results, Chung et al [12], reported an increased incidence of nausea and vomiting with IT neostigmine 25 µg in term parturients. This discrepancy may be explained by the difference in patients' population. Pregnancy is associated with higher potential for cephalad spread of neuraxially injected drugs (39-41), and subsequently increases the incidence of adverse effects [42,43]. Moreover, the preparation of both morphine and neostigmine in a dextrose-containing solution, and maintenance of patients in the sitting position during spinal injection and in a head up position throughout surgery probably contributed to the reduced incidence of nausea and vomiting in our study. These factors were reported to minimize adverse effects through limiting cephalad migration of spinally injected drugs [20,44].

Similar to other adverse effects due to IT morphine or neostigmine administration, nausea and vomiting were reported to occur in a dose-dependent manner [45]. Significantly increased incidence of nausea and vomiting was previously described in association with large doses of both IT morphine (> 200 µg) [46,47], and IT neostigmine (> 50 µg) [44,48].

The incidence of pruritus was higher in the morphine group, in comparison with the neostigmine and control groups. Despite the attemps done to limit central migration of the test drugs [20,44], pruritus represented an inevitable adverse effect following IT morphine administration in some of the studied patients. In accordance with our results, higher incidence of pruritus was described in association with a similar dose of IT morphine

(100 μg) than with either IT neostigmine (25 μg) or IT bupivacaine (12 mg) [12].

Pruritus was reported as one of the most frequent side effects following IT morphine administration [19], especially with doses > 200 μg [14,49]. The mechanism of pruritus may not be fully understood. It is probably not related to histamine release, as histamine antagonists are ineffective in the therapy of pruritus following IT morphine [50]. The activation of mu receptors in the substantia gelatinosa of the spinal cord's dorsal horn may be responsible for pain modulation and other side effects, especially pruritus [51]. This may explain the antipruritic effect of nalbuphine, a specific mu receptor antagonist [49].

In the present study, a commercially available neostigmine preparation containing methyl and propylparabens as antioxidants was used. Previous experimental and human testing of paraben-containing neostigmine in a dextrose solution failed to demonestrate any behavioural or histopathological evidence of neurotoxicity after spinal administration [24,48].

In conclusion, the combination of small dose of neostigmine (25 μg) with spinal bupivacaine anesthesia appears to provide an optimally improved postoperative analgesia after orthopedic procedures. The analgesic efficacy of IT neostigmine (25 μg) was comparable to that of IT morphine (100 μg), and both were superior to bupivacaine alone. The absence of pruritis following IT neostigmine is advantageous, as compared with IT morphine.

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كفاءة حقن جرعة صغيرة من النيوستجمين داخل الغمد الشوكى فى تعديل تسكين الألم بعد جراحة العظام

صممت هذه الدراسة لمقارنة إستخدام عقارى النيوستجمين والمورفين بحقنهما داخل الغمد الشوكى مع عقار البيوبيفاكين لتسكين آلام مابعد عمليات جراحات العظام للطرفين السفليين . أجريت هذه الدراسة على ستين مريضاً تم تقسيمهم عشوائياً إلى ثلاث مجموعات متساوية: المجموعة الحاكمة واستخدم فيها عقار البيوبيفاكين ٥ر١٢ مليجرام ومجموعة المورفين و استخدم فيها عقار المورفين ١٠٠ ميكروجرام مع ٥ر١٢ مليجرام من عقار البيوبيفاكين ومجموعة النيوستيجمين واستخدم فيها عقار النيوستيجمين ٢٥ ميكروجرام مع ٥ر١٢ مليجرام من عقار البيوبيفاكين بالحقن تحت الأم العنكبوتية. تمت مراقبة النبض وضغط الدم ومعدل التنفس ونسبة تشبع الدم بالأكسجين أثناء وبعد العملية الجراحية. أيضاً تمت متابعة مدة ودرجة تسكين الألم بعد العملية، وكذلك حدوث أثار جانبية مثل الغثيان والقئ، الحكة الجلدية، هبوط النبض (أقل من ٦٠ دقة فى الدقيقة)، هبوط متوسط ضغط الدم (أكثر من ٢٠٪ من قيمته قبل التخدير)، هبوط معدل التنفس (أقل من ١٠ فى الدقيقة)، الدوخة والصداع.

أظهرت نتائج هذه الدراسة التساوى بين مجموعتى المورفين والنيوستيجمين بالنسبة لمدة ودرجة تسكين الألم بعد العملية، لكن وجدت فروق ذات دلالة إحصائية بين كلا المجموعتين مقارنة بالمجموعة الحاكمة. كان معدل حدوث الغثيان والقئ متماثلاً بين الثلاث مجموعات، بينما كان معدل حدوث الحكة الجلدية أكثر فى مجموعة المورفين مقارنة بالمجموعتين الأخريين. لم تلاحظ أى أثار جانبية أخرى أثناء فترة الدراسة.

مما سبق يتضح أن إضافة جرعة صغيرة من عقار النيوستيجمين (٢٥ ميكروجرام) مع عقار البيوبيفاكين بالحقن تحت الأم العنكبوتية تبدو مفيدة لتحسين مدة ودرجة تسكين الألم بعد عمليات جراحات العظام .