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Research Article

Adding neostigmine to morphine epidurally lessens the incidence of postoperative urine retention: A comparative study

Hesham Abo El Dahab [a,*], Rania Samir [a], Tarek Menesy [b], Gada Adel [a], Enmar Habib [c]

[a] *Anesthesia Faculty of Medicine – Kasr El Aini, Cairo University, Egypt*
[b] *Anesthesia, Bany Swif University, Egypt*
[c] *Urology, Cairo University, Egypt*

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KEYWORDS

Urine retention;
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Abstract *Introduction:* Postoperative urine retention is a common problem faced with many epidurally administered drugs to relief pain. Morphine was introduced as a potent epidural analgesic, however; its administration is associated with a high incidence of urine retention. Neostigmine had been proposed as an epidural analgesic that lacks major side effects faced with intrathecal neostigmine. However, the effect of the combined use of both drugs upon lower urinary system has not been discussed.
Methods: 100 Patients allocated into 4 equal groups were subjected to inguinal hernia repair under epidural anesthesia. Group I received bupivacaine 10 ml 0.5%, Group II received bupivacaine/morphine 2 mg, Group III received bupivacaine/morphine 2 mg and 5 μg/kg neostigmine and Group IV received bupivacaine and 5 μg/kg neostigmine. Incidences of postoperative urine retention and patients who needed catheterization in each group were recorded. Mean arterial blood pressure, heart rate and incidence of complication (nausea, vomiting, pruritis, hypotension and bradycardia) were recorded. Time for 1st rescue analgesic drug was recorded.
Results: No single patient experienced urine retention in Group IV. Whereas one patient in both Groups I and III versus five patients in Group II suffered from urine retention and required urinary

* Corresponding author.
E-mail address: h_dahab2005@yahoo.com (H.A. El Dahab).

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catheterization. The hemodynamic parameters were comparable between all groups. Time for 1st rescue analgesic drug was prolonged in Group III more than the other groups followed by Groups II, IV and I, respectively.

Conclusion: Addition of neostigmine to morphine epidurally lessened the incidence of postoperative urine retention commonly faced when morphine is used alone with local anesthetic and prolonged the duration of analgesia.

1. Introduction

Urinary retention after surgery is a common problem with an incidence ranging from 5% to 70%. The adult urinary bladder has a capacity of 400–600 ml. When a bladder volume of 150 ml is reached, the first urge to void is felt while at a volume of 300 ml sense of fullness occurs due to activation of the tension receptors in the bladder wall [1]. Urinary retention increases the rate of urinary tract infections. It is treated by urethral catheterization that may further increase the incidence of urinary tract infection [2]. Male gender, increasing age, multiple sclerosis, spinal lesion, a history of bladder outflow problems or surgeries and postoperative epidural analgesia are considered risk factors for the development of urinary retention [3–6]. By acting on the sacral and lumbar nerve fibers, epidurally administered local anesthetics block the transmission of afferent and efferent nervous impulses from the bladder increasing the incidence of postoperative urine retention (POUR). The use of long-acting local anesthetics is associated with a higher incidence of POUR [7–10]. Epidural morphine decreases detrusor strength within 5–15 min reaching its maximum effects within 30–120 min and lasting 10–15 h [11,12]. Thus the addition of opioids to epidural local anesthetics increases the risk of POUR [13]. Neostigmine is a reversible cholinesterase inhibitor. It was used for intrathecal injection as it produces dose dependant analgesia without respiratory depression or hypotension and potentiates the analgesic effects of both narcotic and local anesthetic. Unfortunately, severe gastrointestinal side effects (nausea, vomiting and diarrhea) occurred limiting its routine use. These side effects are thought to be due to rostral spread. However, epidural neostigmine was investigated and found to produce postoperative analgesia for several hours and lack these side effects [14–16]. Being a muscarinic agonist, neostigmine causes an increase in intravesical pressure, leading to hyperactive detrusor contractions [17,18] and parenteral neostigmine was used in reversing postoperative non-obstructive urinary retention [19] and morphine induced retention [20]. While anticholinergic drugs, such as atropine, block detrusor contractions and cause bladder hypotonia resulting in urinary retention [6,21].

This study was designed to assess the value of using epidural neostigmine on bladder function and whether mixing neostigmine with morphine will lessen the incidence of postoperative urine retention commonly faced with epidural morphine or not? Furthermore, to follow-up the analgesic properties as well as the possible side effects.

2. Materials and methods

After approval of the ethical and scientific research committee of the El-Kasr Aini hospital, 100 patients were enrolled in this prospective double blinded study to undergo inguinal hernia repair under epidural anesthesia in the period between January 2008 and December 2009. Male patients aged 20–50 years old with ASA class I, II were included in the study. Patients suffering from bronchial asthma, symptoms of bladder outlet obstruction, history of lower urinary tract surgery (prostate or urethra) and history of neurological disorder (stroke, poliomyelitis, cerebral palsy, multiple sclerosis, spinal lesions, diabetic and alcoholic neuropathy) were excluded from the study aiming to avoid any factor that might increase the risk of development of POUR. Also patients having any contraindication to regional anesthesia (patient's refusal, patients on anticoagulants, skin infection at the site of injection, severe aortic stenosis, severe mitral stenosis, spine anomalies and deformities) and those experiencing accidental dural puncture during the procedure were excluded from the study.

History taking, the international prostate symptom score (IPSS), flowmetry test and ultrasound (U/S) assessment of the lower urinary system, especially post void residual urine estimation were done for all patients as a routine by the urologist. Any patient with IPSS more than 7 or maximum flow rate (Q_{max}) less than 15 ml/s were excluded from the study.

Preoperatively, all patients were instructed how to respond to visual analogue scale (VAS) for pain (10 cm long line) where zero represented no pain at all and 10 represented the worst possible pain. Postoperatively, VAS-P was the chosen method for assessment of pain severity. Upon arrival to the operating room, standard monitors including non-invasive blood pressure, electrocardiogram and pulse oximetry were attached to the patient and baseline readings were collected. An 18 gauge cannula was inserted in the dorsum of the left hand and preload consisted of 10 ml/kg of lactated Ringer's solution before epidural insertion. Epidural catheter was inserted in the lumbar region at L4–L5 interspace under local anesthesia and 3 ml lidocaine was given to all patients as an epidural test dose. Then the patients were randomly allocated into 4 equal groups 25 each by a closed envelope withdrawn by the surgeon.

Group I (bupivacaine group): received 12 ml of the anesthetic admixture which included10 ml of bupivacaine 0.5% and 2 ml normal saline (N/S).
Group II (morphine group): received 12 ml of the anesthetic admixture which included 10 ml bupivacaine 0.5% and 2 mg morphine sulfate in 2 ml normal saline.
Group III (morphine/neostigmine group): received 12 ml of the anesthetic admixture which included 10 ml bupivacaine 0.5% and 1 ml N/S contained 2 mg morphine, 1 ml N/S contained 5 μg/kg neostigmine (Neostigmine was provided from the commercial solution of neostigmine methyl sulfate (Epistigmine®, 2.5 mg/mL; Epico, A.R.E).

Group IV (neostigmine group): received 12 ml of the anesthetic admixture which included 10 ml bupivacaine 0.5% and 2 ml containing 5 μg/kg neostigmine.

Incremental doses given to reach T6 sensory level (assessed by pin brick) in all patients consisted of 3 ml of bupivacaine 0.5%. Plain bupivacaine 0.5% was infused epidurally to all patients after establishment of the level at a rate of 5 ml/h till the end of surgery. Epidural catheters were removed immediately after surgery. In order to keep the blind nature of the study, the drugs were prepared in 20 ml syringes by a blind post-anesthesia care unit nurse according to the instructions written in a closed envelope.

3. Data collected

1. Mean arterial blood pressure (MAP) and heart rate (HR) were measured before insertion of epidural, 5 min after activation and every 15 min till the end of operation.
2. Incidence of urine retention and number of patients needing urinary catheterization in each group. All patients were instructed to void when feel desires or 4 h post operatively when no desire felt, if patient failed to void we waited one more hour. If no volitional voiding occurred and U/S showed bladder volume 400 ml or more we proceeded for urinary catheterization and urine volume was calculated.
3. Time to 1st rescue analgesic was recorded and 1 mg paracetamol intravenously was given when VAS $\geqslant 3$. VAS score was recorded every hour for the 1st 12 h by attending nurse that was blind to the study group.
4. Incidence of complication (nausea, vomiting, pruritis, hypotension, bradycardia and respiratory depression) in each group and how it was managed. Respiratory depression was defined as a respiratory rate <10 breath/min. Bradycardia was defined as heart rate less than 50 beats/min. Hypotension was defined as 20% decrease in mean blood pressure below baseline levels and was managed by ephedrine 9 mg intravenously that could be repeated if necessary. Severe nausea or vomiting was treated with ondanesetrone 4 mg while severe pruritis was treated with chlorpheniramine maleate 10 mg IV slowly every 8 h as required.

3.1. Statistical analysis

Obtained data were presented as means ± SD, ranges, numbers and ratios as appropriate. Categorical data were analyzed using χ^2 test or Fischer exact test as appropriate. Continuous data were analyzed using unpaired *T*-test or univariate two-group repeated measures analysis of variance (ANOVA) with post hoc Dunnett as appropriate. Statistical calculations were performed using SPSS (Version 10, 2002) for Windows statistical package. *P* value <0.05 was considered statistically significant.

4. Results

The demographic data and patients characteristics of the four groups are presented in Table 1 with no significant differences between the groups regarding age, body mass index, ASA physical status, and duration of surgery Table 2.

Intraoperative hemodynamic data, heart rates and mean blood pressures at regular intervals, were not statistically significantly different between the groups Tables 3–5.

Regarding urine retention, a single case occurred in the bupivacaine group as the patient experienced sensation of full bladder with inability to urinate 5 h after surgery and U/S assessment revealed 600 ml urine in the bladder and the problem was solved by urinary catheterization to evacuate the bladder and did not recur again. In Group II five cases of retention occurred, bladder volumes ranged between 480 and 950 ml, patients started to experience difficulty in micturition from 5 to 11 h after surgery. The problem was solved by catheterization once in four patients while the fifth patient developed a second attack of retention 6 h later solved by catheterization. In Group III only one patient suffered from retention 5 h after surgery and the residual volume was 850 ml urine. In Group IV no single patient experienced retention. There was statistically significant differences between Groups II and IV, *P* value 0.028 whereas no statistically significant differences between other groups.

Regarding postoperative nausea and vomiting, only one case suffered from nausea in Group I and this occurred in the recovery room immediately after the end of surgery and was attributed to hypotension and corrected with I.V. injection of 9 mg ephedrine sulfate and 4 mg ondanesetrone intravenously and 200 ml infusion of ringer's lactate over 5 min. In Group II, five cases suffered from nausea and in a single case the nausea was severe and proceeded into vomiting in the 24 h following surgery. Meanwhile, three patients experienced nausea in Group III and only one patient in Group IV and no vomiting occurred in both groups. These cases were treated with ondanesetrone 4 mg and dexamethasone 4 mg I.V.

Regarding pruritis one case occurred in both Groups II and III. No pruritis was observed in the bupivacaine or neostigmine groups.

No respiratory depression was observed in any patient in Groups I or IV, two cases in morphine group and one patient in Group III was managed by supplemental oxygen through face mask. Regarding bradycardia, one patient experienced bradycardia in Group II and another patient in Group III and the bradycardia in those two patients was not associated with

Table 1 Demographic data and patients characteristics.

	Group I bupivacaine	Group II morphine	Group III morphine/neostigmine	Group IV neostigmine
Age (year)	36(4) (27–45)	35(6) (23–47)	37(4) (27–47)	35(5) (25–45)
Body mass index (kg/m^2)	26.3(2.6) (20–32)	25.4(2.8) (21–30)	25.6(2.6) (19–31)	27(3) (21–33)
ASA physical status (I/II)	13/12	11/14	10/15	11/14
Duration of surgery (min)	97(7) (83–110)	99(6) (88–112)	95(7) (82–109)	93(8) (81–107)

Table 2 Preoperative urologic assessment.

	Group I bupivacaine	Group II morphine	Group III morphine/neostigmine	Group IV neostigmine
IPSS	1.28 (1.4)	1.12 (1.2)	1.36 (1.6)	1.08 (1.2)
Q_{max} (ml/s)	24.4 (4.3)	23.8 (4.2)	23.7 (3.8)	23.12 (3.4)
Post void residual urine (ml)	9.4 (7.2)	10.8 (7)	10.6 (7.3)	10 (7.7)

There was no statistically significant difference between the four groups.
Intraoperative hemodynamic data, heart rates and mean blood pressures at regular intervals, were not statistically significantly different between the groups.

Table 3 Heart rate beat/min.

Heart rate beat/minute	Group I bupivacaine	Group II morphine	Group III morphine/neostigmine	Group IV neostigmine
Before Epidural insertion	81.05(11.9)	76.4(5.3)	77.5(10.8)	77.45(6.7)
5 min after	73.5(7.6)	72.1(6.5)	71.7(7.5)	72.1(7.6)
15 min	70.42(3.7)	72.65(6.9)	71.45(5.4)	71.25(5.6)
30 min	71.35(5.3)	70.25(5.7)	70.65(7.3)	72.45(5.9)
45 min	70.3(5.6)	71.2(8.2)	69.15(5.9)	69.65(5.8)
60 min	70.9(5.8)	70.4(8.8)	69.4(6.03)	69.15(6.1)
75 min	69.85(5.01)	70.3(7.5)	71.3(7.8)	71.0(7.7)
90 min	68.65(5.18)	69.9(4.66)	70.5(8.2)	70.85(8.08)
105 min	71.6(7.5)	68.45(5.88)	70.8(7.21)	70.6(7.8)

Table 4 Mean arterial blood pressure (mmHg).

Blood pressure mmHg	Group I bupivacaine	Group I morphine	Group III morphine/neostigmine	Group IV neostigmine
Before insertion	76.45(5.22)	77(5.35)	78.35(5.14)	77.5(5.53)
5 min after	73.55(5.44)	74.2(3.6)	75.25(5.36)	73.5(4.7)
15 min	73.65(3.55)	74.15(4.14)	75.6(4.56)	74.1(4.11)
30 min	74.7(3.04)	75.3(3.26)	75.05(4.34)	76.2(4.09)
45 min	75.35(4.98)	75.6(4.38)	76.05(4.93)	74.45(4.34)
60 min	75.75(4.21)	74.25(3.9)	75.1(3.16)	74.85(4.5)
75 min	75.56(2.5)	74.75(3.02)	74.6(2.8)	74.2(3.7)
90 min	74.5(5.6)	73.45(5.1)	73.9(6.64)	74.4(3.91)
105 min	73.9(6.03)	73.35(4.3)	74.1(7.03)	75.25(5.37)

Table 5 Incidence of postoperative complications.

	Group I bupivacaine	Group II morphine	Group III morphine/neostigmine	Group IV neostigmine	*P*
Urine retention	1/25	5/25*	1/25	0/25*	0.028*
Pruritis	0/25	1/25	1/25	0/25	0.564 NS
PONV	1/25	5/25	3/25	1/25	0.180 NS
Respiratory depression	0/25	2/25	1/25	0/25	0.286 NS
Hypotension	1/25	1/25	1/25	1/25	1.000 NS
Bradycardia	0/25	1/25	1/25	0/25	0.564 NS

* Group II statistically significant relative to Group IV.

hemodynamic instability and lasted for a short period and hence we did not use atropine. Regarding hypotension one patient in each group suffered from hypotension and the condition was managed with 9 mg ephedrine sulfate I.V. Table 6.

5. Discussion

Urine retention is a devastating problem commonly faced with epidurally administered narcotic adjuvants especially morphine [22]. Epidurally administered neostigmine has been recently used to prolong duration of analgesia and augment the local anesthetic effects.

The main finding of our study was that the combined use of neostigmine and morphine epidurally lessened the incidence of urine retention faced when morphine is used alone and enhanced its analgesic effect. In the present study we tried to exclude any factor that might precipitate any increase in the incidence of urine retention aiming that our results to be a sole reflection of the drugs administered. Our results showed that only the patients that were assigned to neostigmine group

Table 6 Time for 1st rescue analgesic (min).

	Group I bupivacaine	Group II morphine	Group III morphine/neostigmine	Group IV neostigmine
Time in minutes	160(12)	710(63)[b]	824(41)[a]	524(39)[c]

There were statistically significant differences between the four groups.
[a] Group III statistically significant relative to the other three groups.
[b] Group II statistically significant relative to the Groups I and IV.
[c] Group IV statistically significant relative to Group I.

did not experience any degree of POUR. Moreover, the addition of neostigmine minimized the incidence of POUR in patients who received epidural morphine. To best of our knowledge, although parenteral neostigmine has been used as a rescue therapy for the treatment of POUR no previous studies tested its effect when administered epidurally. Our results go with the result of Omais et al. [23], who studied the side effects of epidural neostigmine and morphine and found five patients in the morphine group who complained of urinary retention out of fifteen (incidence 33%) and three of them required a urinary catheter while in the morphine/neostigmine group, two patients out of 15 (incidence 14%) complained of urinary retention. Agarwal et al. [24] concluded that epidural neostigmine is effective in providing analgesia and also it led to the development of detrusor overactivity and decrease in bladder capacity without any effect on voiding function so it might help to avoid any voiding difficulty.

As noted from many previous studies, epidural analgesia increases the incidence of postoperative urine retention. Walts et al. [25] found an increase in the incidence of postoperative urinary retention from 24% to 62%.with the use of epidural analgesia in patients undergoing total hip arthroplasty. Moreover, Gedney and Liu [6] studied the side effects of epidural opioids and reported an incidence of 55% urine retention in patients who underwent total joint arthroplasty. We could explain the lower incidence of our study that ranged from 4% in Groups I and III to 20% in Group II by the different selection criteria of our patients, different age group (less than 50 years) and also different type of surgery.

The analgesic efficacy of epidural administered neostigmine has been expressed by multiple authors. Some have found a beneficial effect, while others could not elucidate any effect. Our results showed that neostigmine prolonged the time needed for 1st rescue analgesic in neostigmine group relative to the local anesthetic group and also the combined use of neostigmine with morphine prolonged that time statistically than morphine alone. In line with our results was that of Nakayama et al. [15] who found that neostigmine produced analgesia in a dose dependant manner as 10 μg/kg neostigmine produced more durable analgesia than 5 μg/kg in female patients who underwent abdominal hysterectomies under epidural anesthesia.

Contrary to our results was that of Roelants et al. [26] who demonstrated that epidural neostigmine given as a single dose up to 4 μg/kg did not appear to provide an analgesic benefit during normal labor. However, this was explained by the fact that labor pain was visceral in origin, while other studies including ours were testing neostigmine in patients suffering from somatic pain. More recently, Ross et al. [27] demonstrated that epidural neostigmine up to 80 μg was effective in labor pain as it reduced the epidural bupivacaine requirement by 25% and lacked any significant side effects upon mother or fetus apart from mild sedation. Also Lauretti et al. [28], proved that the addition of epidural neostigmine to lidocaine produced dose independent analgesia.

In the current study, the hemodynamic parameters (heart rate and mean arterial blood pressure) did not vary among the four groups throughout the study protocol. Consistent with this view, Chung et al. [29], found that no significant adverse hemodynamic effects in maternity patients when neostigmine administered intrathecally during cesarean section. In line with our results was that of Omais et al. [23], found that the mean blood pressure and heart rate that were measured at regular intervals were the same in all groups in their patients receiving epidural morphine and neostigmine together with spinal anesthesia for knee orthopedic surgery.

Our results showed that only one case in neostigmine group suffered from nausea and vomiting postoperatively and this goes in line with the results of Omais et al. [23] who found that although PONV were very distressing side effects after intrathecal neostigmine, no adverse effects were noted after its epidural administration. Moreover, Eisenach [30] reported that the incidence of nausea and vomiting was very infrequent and was not greater than that found in the control group. Also our results showed that in the M/N group 3/25 suffered from PONV while in the morphine group five patients suffered from PONV. It also goes with the results of Roelants et al. [26] and the results of Leuretti et al. [28] who found epidural administration of neostigmine lacked these side effects. Therefore, we suggest that those cases that experienced nausea and vomiting were mainly related to the use of epidural morphine.

Regarding pruritis, it occurred only in the two groups, M and MN groups, where morphine was administered epidurally and was not present in any patients in the other two groups and also it was lower in the combined group. This goes with the result of Ross et al. [27] who found that the incidence of pruritus was significantly lower in the morphine/neostigmine group than in the morphine group. This study needs to be confirmed by other studies using larger number of patients to support the accuracy of our hypothesis. Conclusion: the use of epidural neostigmine is not associated with urine retention; on the contrary it decreased the incidence of urine retention faced with morphine and prolonged its analgesic effects.

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