

## **A Randomized Clinical Trial Comparing the Effect of Different Techniques of Selective Spinal Anaesthesia in Cystoscopic Procedures**

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### **ABSTRACT**

**Background:** Selective spinal anaesthesia is commonly used in cystoscopic procedures. Addition of different analgesic drugs to spinal bupivacaine anaesthesia could potentiate its analgesic effects.

**Aim of the study:** This work was designed to compare the effect of small dose of neostigmine (50 µg) or fentanyl (25 µg) when used as an adjuvant to spinal bupivacaine anaesthesia.

**Patients and Methods:** The study included 45 patients, ASA I or II scheduled for cystoscopic procedures at NCI. The patients were randomly allocated into 3 groups, 15 patients each, according to the test solution added to spinal bupivacaine anaesthesia: Group I, (control group) where patients received 1 ml of IT saline, while patients in group II (neostigmine group) received 50 µg. IT neostigmine. In group III, patients received 25 µg. IT fentanyl as an analgesic adjuvant to bupivacaine anaesthesia.

**Results:** Neostigmine 50 µg added to spinal bupivacaine anaesthesia significantly increased the duration of sensory and motor block. It also increased the time until discharge. Sedation and nausea were the most common side effects. Fentanyl 25 µg added to the same spinal anaesthesia, did not affect motor block, while potentiating the sensory block criteria.

**Conclusion:** Selective spinal anaesthesia (SSA) is appropriate and safe for use in outpatient procedures. Neostigmine or fentanyl added to IT bupivacaine may improve the quality of spinal anaesthesia with low incidence of adverse effects.

**Key Words:** *Selective spinal anaesthesia - Bupivacaine - Neostigmine - Fentanyl - Cystoscopic procedures.*

### **INTRODUCTION**

Our expanding knowledge in the field of pain transmission and modulation gave rise to the introduction of novel analgesic drugs in clinical practice. The direct application of re-

ceptor-specific drugs at the spinal cord could potentially interrupt specific pain pathway and limit systemic side effects [6]. Over the past decade, there was an intense interest in the use of analgesic drugs as an adjuvant to spinal bupivacaine anaesthesia. Although these drugs can potentiate the analgesic effect and decrease the rate of failure of spinal anaesthesia, yet they may have their own side effects which limit their use [11].

Selective spinal anaesthesia (SSA), using lower doses of intrathecal agents with or without intrathecal (IT) adjuvants, has been used to provide spinal anaesthesia with greater selectivity and rapid return of function [23].

In outpatient cystoscopic procedures, SSA may be considered the commonest used technique, because it may help early mobilization and recognition of symptoms associated with overhydration and bladder perforation [17].

Hyperbaric bupivacaine is appropriate for rapid anaesthetic recovery and cardiovascular stability. Intrathecal adjuncts such as opioids, vasoconstrictors and  $\alpha_2$ -adrenergic agonists may be added [18]. Lipophilic opioids (e.g. Fentanyl) are increasingly being administered intrathecally as adjuncts to local anaesthetics. They enhance spinal anaesthesia without prolonging motor recovery and discharge time [8].

Recent research has shown the involvement of neostigmine in pain modulation and its safe use at the spinal level. Pan et al., [22] demonstrated that neostigmine added to spinal anaesthesia may enhance the sensory blockade and

improve the quality of spinal anaesthesia with few side effects.

The aim of the present study was to assess the effect of small doses of neostigmine or fentanyl added to spinal bupivacaine anaesthesia on sensory block, motor block and side effects.

### PATIENTS AND METHODS

Forty five patients, ASA I or II, scheduled for cystoscopic urological procedures under spinal anaesthesia were included in the study. Patients with deformities of the vertebral column, infection at the site of lumbar puncture or neurological disease were excluded.

The study protocol was approved by the ethical committee of NCI, Cairo University, and written informed consents were obtained from all patients.

Before lumbar puncture, an IV cannula was inserted. All patients were premedicated with midazolam 0.08 mg.Kg IV (Dormicum) and 1 mg grainsetron (Kytril) (Hoffmann La Roche). Then circulatory preload by 500 ml 0.9% saline (NaCl) was started followed by an infusion of 6-10 ml.Kg<sup>-1</sup>.h<sup>-1</sup>.

Spinal anaesthesia was performed at L<sub>3-4</sub> interspace with the patient in the sitting position using 22 gauge spinal needle (B-brown) with an introducer. Free flow of cerebrospinal fluid was verified before and after injection of the anaesthetic solutions. All patients remained in the sitting position for 20 minutes after injection. The test and anaesthetic solutions were kept in separate syringes. Test solutions were injected intrathecally followed by 3 ml of hyperbaric bupivacaine 0.5% (heavy marcaine - Astra). Patients were randomly allocated into 3 groups according to the test solution injected

Patients in the control group received intrathecal injection of 1 ml of 0.9% saline (saline group), while patients in group II (neostigmine group) received 50 mg neostigmine (amostigmin - amoun). In group III (Fentanyl group), patients received 25 µg fentanyl (fentanyl citrate janssen). In the operating room, patients were monitored with electrocardiography, automated oscillometry and pulse oximetry.

Hypotension, defined as systolic blood pressure (SBP) < 90 mm.Hg or less than 70% of the preanaesthetic value was treated with ephedrine incremental doses of 2 mg intravenously.

Bradycardia (< 50 beats/min or decreased heart rate more than 20% from the initial value) was treated by intravenous atropine 0.5 mg.

Respiratory depression was defined as a respiratory rate of < 8 breaths/ min and/or oxygen saturation < 85% in room air.

Severe nausea and vomiting were treated by IV metoclopramide 10 mg.

The level of sensory block, defined as the loss of sharp sensation by using a pinprick test was recorded bilaterally at the midclavicular line. Motor block was assessed by modified Bromage scores [11] where:

- 0- No motor loss.
- I - Inability to flex the hip.
- II- Inability to flex the knee.
- III- Inability to flex the ankle.

Complete motor recovery was assumed when the modified Bromage score was zero.

*Sedation was assessed using a four point scale [21] where:*

- 1- Awake.
- 2- Drowsy but responsive to verbal stimulus.
- 3- Drowsy but responsive to physical stimulus.
- 4- Unresponsive to verbal and physical stimulus.

All tests were performed at 15-min intervals from the time of injection until the motor block had completely recovered.

The severity of postoperative pain was measured using a 10 cm visual analogue scale where (0 = no pain, 10 = excruciating pain) and a verbal rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). Rescue analgesia was administered when the patient expressed a need for additional analgesia or signs of ineffective analgesia (VAS > 4 or VRS > 2) were recorded by the anaesthetist. The non steroidal anti-inflammatory drug, diclofenac 75 mg (Voltaren, Roche) was given IM.

Adverse effects including pruritis, sweating, headache, backache or transient neurological symptoms were recorded.

Headache was classified as postdural puncture headache (PDPH), if it was aggravated by erect or sitting position, relieved by lying flat,

mainly occipital or frontal and increased on coughing, sneezing or straining.

Transient neurological symptoms (TNS) were defined as pain and/or dysesthesia in the back, buttocks, and legs or pain radiating to the lower extremities after initial recovery from spinal anaesthesia and resolved within 72 hours.

The discharge criteria from the recovery room were stable vital signs, return of pin prick sensation to dermatomal level S<sub>2</sub>, complete resolution of motor block (patients able to walk), no nausea, vomiting, pain or bleeding.

The following times were recorded after intrathecal injection of local anaesthetic solution.

- A- Time from IT drug injection to L<sub>2</sub> dermatome sensory regression.
- B- Time to patient's first rescue analgesics administration.
- C- Time to complete recovery of lower limb motor function (Bromage scale: 0).
- D- Time until discharge.

Comparative study was done between each technique of selective spinal anaesthesia and standard spinal bupivacaine anaesthesia used for outpatient urological procedures.

Statistical analysis was done using SPSS-11. Means and standard deviations were used as a summary of quantitative data. A I-tail t-test was used for comparison of group II and III with controls. The threshold of significance was fixed at the % level ( $p = 0.05$ ).

## RESULTS

The study groups were comparable with respect to age, weight and duration of the procedure, as demonstrated in table (1). The number of segments blocked was similar in the three groups.

The mean time to reach maximum anaesthetic level at T8 was longer in the saline group as compared to the other 2 groups. However, this was not proved to be statistically significant ( $p > 0.05$ ). There was no significant difference in comparison with the control group as regards onset of grade III motor block.

The time taken for sensory block regression to L<sub>2</sub> dermatome was significantly higher in the

Neostigmine group ( $p = 0.01$ ), compared to the saline group but not with Fentanyl ( $p > 0.05$ ).

Spinal neostigmine was as effective as fentanyl and significantly prolonged the time to the first analgesic administration compared to the saline group. Both neostigmine and fentanyl groups differed significantly from the saline group ( $p = 0.05$  &  $p < 0.001$  respectively) as demonstrated in table (2) and Fig. (1).

As regards characteristics of motor block, there was no statistical difference between both saline and fentanyl group ( $p > 0.05$ ). On the other hand, neostigmine group differed significantly from the saline group as regards the time needed for complete recovery of motor block ( $p < 0.001$ ).

Neostigmine was shown to prolong the motor block of bupivacaine, and significantly prolong the time until discharge ( $p < 0.001$ ) when compared to the saline group.

Patients in fentanyl group, did not differ from the saline groups except for time until discharge, which was significantly longer than the saline group ( $p < 0.001$ ) [Table (2) and Fig. (1)].

None of the patients needed supplementation of analgesia during the operation and the surgeons were satisfied with the intensity of the motor block.

The mean blood pressure and heart rate measured every 15 min after spinal injection, are demonstrated in figs. (2,3) and tables (3, 4).

Two patients in group I and one patient in group II had hypotensive episodes. The blood pressure returned to normal after IV injection of ephedrine 5 mg and an infusion of 500 ml of NaCl 0.9%. Three patients needed treatment for bradycardia.

There were no detectable differences in oxygen saturation or respiratory rate between groups.

The most common side effect was sedation, it was seen primarily during the first 2 hours after surgery. Profuse sweating was observed only in one patient in neostigmine group.

In all patients who received fentanyl, pruritus was the most distressing complication (2 pa-

tients) (Table 5). Nausea and vomiting were most common in neostigmine group, in spite of premeditation with grainsetrone (Kytril, 1 mg), which may have effect in reducing the incidence of vomiting in the three studied groups.

Nausea was more in the neostigmine group (6 patients). Only one patient experienced an episode of vomiting in the postoperative period.

No neurological sequelae were observed in the immediate postoperative period.

Table (1): Patients' characteristic and perioperative data.

	Group I Saline	Group II Neostigmine	Group III Fentanyl
Number of patients	15	15	15
Sex M/F	11 / 4	10 / 5	13 / 2
Age (Y)	54.3±8.1	56.9±4.7	58.7±7.2
Weight (Kg)	67.2±14.9	64.9±12.7	69.4±10.8
Test drug used	Saline	Neostigmine 50 µg.	Fentanyl 25 µg
Duration of cystoscopic procedure (min)	24.7±12.5	28.3±11.9	26.9±16.1
Maximum level of sensory block (median & range)	T <sub>8</sub> (6 - 10)	T <sub>8</sub> (4 - 10)	T <sub>7</sub> (4 - 10)
Time from IT drug injection to highest sensory level (min)	8.2±3.1	7.9±2.8 <i>p</i> > 0.5 N.S	7.4±2.9 <i>p</i> > 0.5 N.S
Onset of grade III motor block (min)	8.4±3.6	7.8±2.9 <i>p</i> > 0.5 N.S	8.9±3.1 <i>p</i> > 0.05* N.S

\* Values are mean ±SD or median (range), NS: not significant

Table (2): Characteristic of spinal block of bupivacaine anaesthesia with different test drugs with comparison to control group.

	Group I Saline	Group II Neostigmine	Group III Fentanyl
A- Time to L2 dermatome sensory regression (min)	126.4±39.2	156.9±32.7 * <i>p</i> = 0.01	138.2±28.3 <i>p</i> > 0.05
B- Time to patient's first rescue analgesics administration (min)	164.1±10.9	173.7±18.2 <i>t</i> = 1.75 <i>p</i> = 0.05	197.0±21.8 <i>t</i> = 522 <i>p</i> < 0.001*
C- Time for complete recovery of the motor block grade 0 bromage scale (min)	178.1±47.1	302.7± 64.7 <i>t</i> = 6.03 <i>p</i> < 0.001*	181.4±34.8 <i>t</i> = 0.218 <i>p</i> > 0.05
D- Time until discharge (min)	196.9±42.9	315.9 + 86.3 <i>t</i> = 4.78 <i>p</i> < 0.001*	270.8±74.3 <i>t</i> = 3.33 <i>p</i> < 0.001*

Values are mean ± SD \* Significant *p* < 0.05 NS not significant

Table (3): Changes in mean arterial blood pressure (mm.Hg) of the three groups during the study period.

	Group I Saline	Group II Neostigmine	Group III Fentanyl
Pre perative	90.6±8.3	91.4±10.5	88.2±6.3
15 min	72.7±6.8	88.6±6.4*	69.7±9.4
30 min	78.3±4.1	86.8±8.2*	79.8±10.2
45 min	78.9±11.7	87.9±6.1*	76.3±4.9
60 min	81.3±7.4	89.9±9.6*	79.7±6.4
120 min	91.5±7.7	92.3±5.2	89.6±12.3
240 min	90.8±18.6	91.9±3.6	91.1±10.4

\* Figures are mean ±SD

\* Significant when compared to group I *p* < 0.05

Table (4): Changes in heart rate (beat.min<sup>-1</sup>) of the three groups during the study period.

	Group I Saline	Group II Neostigmine	Group III Fentanyl
Pre perative	79.3±11.7	76.3±12.6	77.8±9.4
15 min	78.2±6.4	74.1±4.8*	79.2±5.3
30 min	76.6±7.3	66.4±7.9*	78.1±4.4
45 min	76.1±4.2	67.9±11.3*	76.8±3.8
60 min	76.3±3.9	72.3±8.1*	76.9±4.9
120 min	76.9±9.5	77.6±4.9	78.9±3.6
240 min	73.8±16.9	79.2±12.5	78.3±11.4

\* Figures are mean ±SD

\* Significant when compared to group I *p* < 0.05

Table (5): Side effects in the three studied groups.

	Group I Saline	Group II Neostigmine	Group III Fentanyl
Respiratory depression	—	—	—
Pruritus	2	—	2
Shivering	—	1	—
Sweating	—	1	—
Nausea	—	6	3
Vomiting	—	1	—
PDPH	—	—	—
TNS	—	—	—
Sedation score more than 2	—	8	2

Figures are number of patients

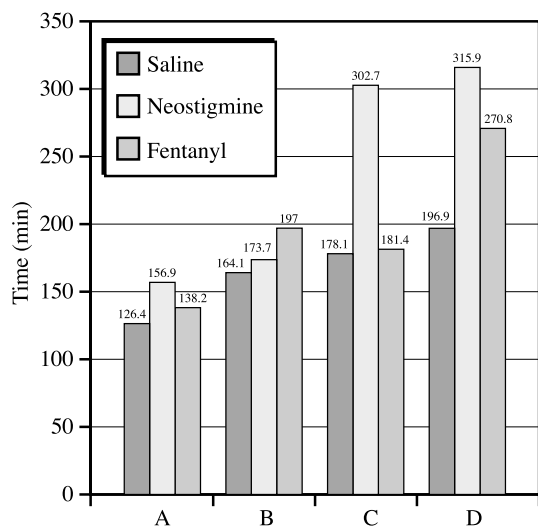


Fig. (1): Characteristic of spinal block of bupivacaine anaesthesia with different test drugs as demonstrated in table (2).

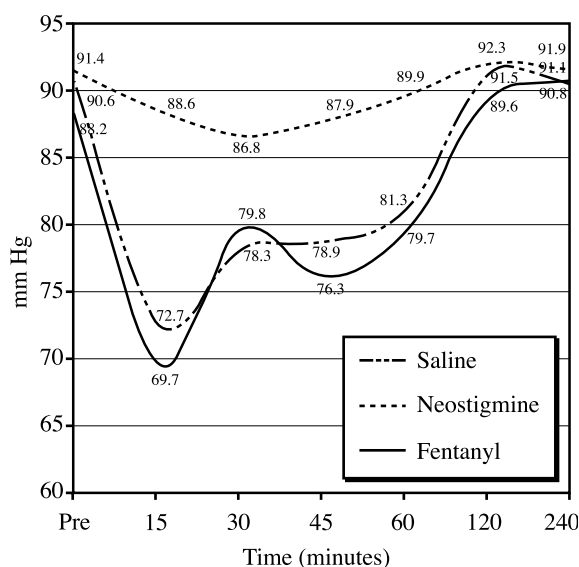


Fig. (2): Changes in mean arterial blood pressure (mm Hg) of the three groups during the study period.

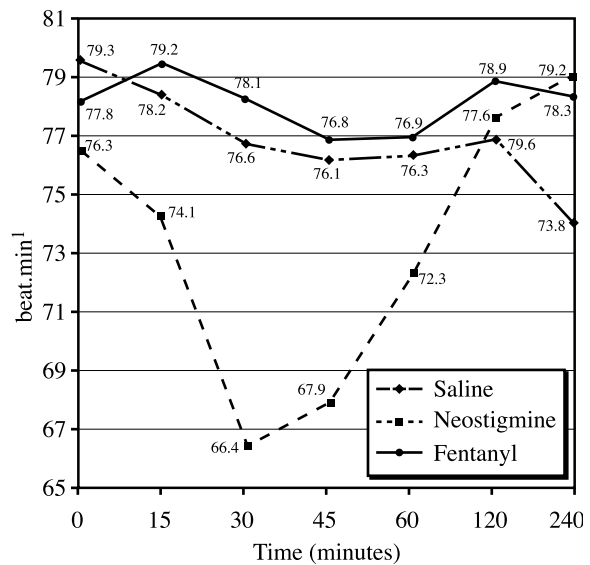


Fig. (3): Change in heart rate (beat min<sup>-1</sup>) of the three groups during the study period.

### DISCUSSION

Spinal bupivacaine has been widely used in surgical procedures lasting less than one hour [7]. It may help to prevent complications associated with delayed immobilization. Other advantages include preference by surgical staff, avoidance of general anaesthesia in elderly patients and a general comfortable recovery which are suitable for ambulatory patients [15].

Optimal pain relief with minimal side effects can be achieved by additive or synergistic effects of different analgesic drugs added to spinal bupivacaine anaesthesia (SSA). The present study was undertaken to investigate the efficacy of hyperbaric bupivacaine and try to maximize its effect using additive analgesic drugs (neostigmine or fentanyl).

The results demonstrated similar levels of sensory block achieved in the three experimental groups, suggesting that the spread of IT bupivacaine was not affected by the addition of either drugs. There was no statistically significant difference between groups II or III when compared to the saline group as regards the time taken to reach highest sensory level. The time taken for sensory block regression to L2 and the time to the first analgesic administration were significantly longer in the neostigmine group when compared to the saline group.

Our results are in accordance with the results reported by Lauretti et al. [13] who demon-

strated the analgesic effect of 50 mg intrathecal-ly administered neostigmine and its potentiation of IT morphine analgesia.

Chung et al., [5] demonstrated that combination of IT neostigmine and morphine produces better analgesia than morphine alone.

Intrathecal neostigmine produces dose-dependent analgesia by inhibiting the breakdown of acetylcholine in the dorsal horn and spinal meninges [1]. Bauoziz and his colleagues [2] hypothesized that pain and surgical trauma enhance spinal cholinergic tone. This would increase acetylcholine cerebrospinal fluid concentration and improve its bioavailability at cholinergic nerves within the spinal cord [20]. Acetylcholine may cause analgesia through direct action on spinal cholinergic muscarinic receptors M1 and M3 and nicotinic receptor subtypes, in addition to stimulation of the release of the second messenger nitric oxide [14]. Xu et al. [26], provided evidence that nitric oxide is necessary for the expression of analgesia secondary to cholinomimetic drugs.

The current results demonstrated that the addition of 50 µg neostigmine prolonged motor block of spinal bupivacaine anaesthesia. This effect could be explained by acetylcholine-mediated reduction in motor neuron outflow in addition to the potential direct inhibition of motor activity by neostigmine.

Urological cystoscopic procedures require adequate degree of muscle relaxation as unexpected movement of the patients may predispose to complications (e.g. bladder perforation).

The spinal haemodynamic effects of it neostigmine are explained by its action on M2 muscarinic receptors in the intermediolateral cell column [19]. Spinal neostigmine increases the activity of preganglionic sympathetic neurons, counteracts the sympatholytic effects of local anaesthetics and prevents hypotension during spinal anaesthesia [25].

In the present study, there was no significant change in heart rate and mean blood pressure in all groups, Klamt et al. [12] observed lower incidence of hypotension combined with spinal anaesthesia after intrathecal neostigmine injection. Drugs with pharmacological profile similar to that of neostigmine (e.g. isobaricity and water solubility) could easily spread to su-

praspinal level reaching the brain stem when injected into the lumbar cerebrospinal fluid.

Carp et al. [3] suggested that aggravation of side effects depends on the drug action at the brain stem level. Sweating above the level of sensory block is a sign of sympathetic activity. Hood et al. [9] ascribed the vomiting effect to an action of neostigmine on the brain stem, since a hyperbaric solution of this drug produces analgesia limited to the lower limbs without producing nausea or vomiting. Sedation observed in this study was mild and could be explained also by cephalic spread of neostigmine to the brain stem. These results are in agreement with the results described by Hood et al. [10].

IT fentanyl was also found to potentate the analgesic effect of local anaesthetic and prolong the time to the first analgesic administration when compared to the saline group.

Several investigators have evaluated IT fentanyl with spinal local anaesthetic drugs. In accordance with our results, Liu et al. [16] found that fentanyl prolonged sensory anaesthesia without affecting the motor function.

Addition of an intrathecal lipid soluble opioid (fentanyl) is gaining popularity, not only because of its beneficial analgesic effects, but also because of improved pulmonary functions and stress response detected after its use in abdominal surgery [15].

Varassi et al. [24] demonstrated that the subarachnoid administration of 25 µg of fentanyl during spinal anaesthesia does not alter respiratory parameters in elders. In our study, absence of respiratory complications in fentanyl group agree with their results.

In the present study, pruritus was the most common complication after IT fentanyl. However, it was well tolerated and did not need treatment. These results are consistent with those of Lui et al. [16] who demonstrated that the addition of 20 mg of fentanyl intrathecally is associated with high incidence of pruritus.

Spinally administered fentanyl may exert its analgesic effect through binding with opioid receptors in the dorsal horn of the spinal cord.

Both systemic absorption and cephalad spread in CSF would allow for fentanyl interaction with supraspinal receptors. Several investi-

gators have evaluated the analgesic effect of IT fentanyl when combined with spinal local anaesthetics [4,8].

The results of the current study demonstrated significant prolongation of time till discharge in both neostigmine and fentanyl groups when compared to group I ( $p < 0.001$ ). These results were in agreement with the results observed by Kathirval et al. and Klamt et al. [11,12]. They documented that IT adjuvant drugs provide better operative condition at the expense of prolonged discharge time.

Sedation, nausea and prolongation of motor block were the causes of delayed discharge in the neostigmine group, while pruritis and respiratory monitoring were the main concern in the fentanyl group.

However, the success of day-case surgery depends on effective control of postoperative pain and patients' satisfaction after discharge, which were fulfilled in both neostigmine and fentanyl groups.

In conclusion, selective spinal anaesthesia, using small doses of spinal neostigmine or fentanyl can modify the spinal block criteria of bupivacaine anaesthesia. Spinal neostigmine enhances both sensory and motor block. Also, it counteracts the hypotension induced by spinal anaesthesia. Sedation and nausea were the most common side effects. Spinal fentanyl provides adequate analgesic effects without prolongation of the motor block.

Both drugs improve the quality of spinal anaesthesia on the expense of increased side effects.

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