

# Comparison of analgesic activity of the addition to neostigmine and fentanyl to bupivacaine in postoperative epidural analgesia

Selcen Tekin, MD, Ismet Topcu, MD, Neriman Z. Ekici, MD, Husnu Caglar, MD, Tuna Erincler, MD.

## ABSTRACT

**Objectives:** To compare the analgesic and side effects of bupivacaine in combinations with neostigmine and fentanyl using patient-controlled-epidural analgesia (PCEA) methods in the postoperative period after abdominal hysterectomy.

**Methods:** Seventy-five adult American Society of Anesthesiologists physical status I-II patients, aged 18-65 years were included in the study. The study took place in Celal Bayar University Hospital, Turkey between 2003-2004 years. After preoperative epidural catheterization, the patients were operated under general anesthesia. After surgery, the patients were randomly allocated in a double-blinded manner to receive PCEA and divided into 3 groups: Group B: 0.125% bupivacaine, Group N: 0.125% bupivacaine plus neostigmine  $4 \mu\text{g kg}^{-1}$  and Group F: 0.125% bupivacaine plus  $1 \mu\text{g kg}^{-1}$  fentanyl solutions (10 mL loading dose, 5 mL bolus dose, 10 min lockout time, 30 mL in 4 hour limit). During the following 24 hours,

hemodynamic parameters, pain score using visual analog scale, total analgesic consumption, additional analgesic requirements, sedation, satisfaction, nausea scores and probable side-effects were evaluated.

**Results:** Total analgesic consumption was  $143.7 \pm 7.2$  mL in Group B,  $123.4 \pm 6.2$  mL in Group N and  $106 \pm 8.3$  mL in Groups F. The mean value in Group F was significantly lower than Group N and Group B ( $p < 0.05$ ), and was lower in Group N than Group B. Visual analog scale scores were lower in Group F than other groups ( $p < 0.05$ ). There were no differences in side effects between all groups.

**Conclusions:** Fentanyl and neostigmine by the PCEA method can be used safely for postoperative analgesia after gynecologic surgery. They increase analgesia quality and satisfaction without an increase in side effects.

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Patient-controlled epidural analgesia (PCEA) provides effective postoperative analgesia when properly used.<sup>1</sup> In addition, it may improve outcome of patients after major abdominal surgery.<sup>2,3</sup> Owing to this method is to obtain steady plasma concentration and prevent alterations. Consequently, better analgesia and patient's comfort are provided while avoiding from side-effects.<sup>4</sup> Patient-controlled epidural analgesia with local anesthetics is effective

in controlling postoperative analgesia after abdominal surgery. Likewise by lowering doses, side-effects of local anesthetics (hypotension, motor weakness, urine retention, and decubitus wound due to sensorial block to skin) may be reduced.<sup>5,6</sup> Therefore, a combination of local anesthetics and opioids are commonly used after gynecological surgery.<sup>7,8</sup> They cease pain in different mechanisms. Local anesthetics effect nerve axons while opioids spinal receptors. Analgesia

From the Department of Anesthesiology (Tekin, Topcu, Erincler, Ekici), and the Department of Obstetrics and Gynecology (Caglar), Faculty of Medicine, Celal Bayar University, Manisa, Turkey.

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Address correspondence and reprint request to: Dr. Selcen Tekin, Guzelyurt Mah. Ingolstadt Cad, Anadolu Konutları No:11, 45030, Manisa, Turkey. Tel. +90 (505) 2555996. Fax. +90 (236) 2370213. E-mail: selcengeraslan@hotmail.com

begins rapidly, lasts longer and it is deeper in patients receiving low doses of local anesthetics and opioids. Lesser motor block occurs rather than single use of these 2 drugs.<sup>9,10</sup> Neostigmine, a synthetic drug, is temporarily inhibiting acetylcholinesterase (ACh). It has been demonstrated that, it increases acetylcholine in the cerebrospinal fluid (CSF) and provides antinociception.<sup>11</sup> Neostigmine provides analgesia in animals and in humans by applying through spinal route.<sup>11,12</sup> However, there are limited studies regarding the efficiency of epidural neostigmine for the purpose of postoperative analgesia.<sup>13-16</sup> The aim of this randomized, double-blinded study was to assess the analgesic efficacy and side effects of epidural administered bupivacaine with neostigmine and fentanyl using PCEA in the postoperative period after abdominal hysterectomy (TAH).

**Methods.** This study was approved by the University Hospital Ethics Committee. Seventy-five adult American Society of Anesthesiologists (ASA) physical status I-II patients, aged 18-65 years scheduled for elective TAH were selected for this prospective, randomized and double-blinded study. The study took place in Celal Bayar University Hospital, Turkey between 2003-2004 years. The patients who had drug hypersensitivity, coagulation defects, neurological problems, cooperation problems and contraindications for epidural analgesia were excluded. Prior to operation, patients were informed regarding the procedure and PCEA device. All patients were taken into the operating room unpremedicated. At operation day, the patients were placed in the supine position, by inserting an 18 G cannula to the antecubital vein; Lactated Ringer's solution was started at 10 mL kg<sup>-1</sup> h<sup>-1</sup>. Electrocardiograph, heart rate (HR), systolic-diastolic-mean arterial pressure (SAP, DAP, MAP), peripheral oxygen saturation (SpO<sub>2</sub>) and end-tidal CO<sub>2</sub> were monitored. Epidural catheter replacement was planned to all patients through L2-3 or L3-4 epidural space before operation. Epidural catheter (B Braun Melsungen AG, Perifix®) was placed to the epidural space by using loss-of-resistance technique with saline and advanced through 3-4 cm into the epidural space. Test dosage with 3 mL of 1.5% lidocaine was used in order to confirm the correct place of the tip of the catheter. Induction of anesthesia was achieved with fentanyl 2 µg kg<sup>-1</sup>, thiopentone 5 mg kg<sup>-1</sup> and vecuronium 0.1 mg kg<sup>-1</sup>. Standard general anesthesia was maintained with sevoflurane 2-4% and nitrous oxide 60% in oxygen and vecuronium for muscle relaxation. No opioid or analgesic was used for maintenance. After surgery, patients were admitted to the post-anesthetic care unit (PACU). They were

divided into 3 groups as randomized (envelope randomization) and double-blinded. Each patient received a PCEA for postoperative analgesia (Abbott Pain Management Provider®, North Chicago, IL, USA). Patient-controlled epidural analgesia solutions were prepared as: Group B bupivacaine 0.125%, Group N 0.125% bupivacaine plus neostigmine 4 µg kg<sup>-1</sup>, Group F 0.125% bupivacaine plus fentanyl 1 µg kg<sup>-1</sup> within 100 mL saline. Patient-controlled analgesia (PCA) pump was programmed as 5 mL bolus dose, 10 min lockout (no basal infusion, 30 mL in 4 hour limit) and 10 mL loading dose (from PCA solution). Duration of surgery and stay in PACU were recorded. Heart rate, SAP, DAP, MAP, SpO<sub>2</sub>, and respiration rate (RR) were recorded at 1, 3, 6, 12, and 24 hour postoperatively. Quality of the patients' pain was evaluated by visual analogue scale (VAS; 10 cm scale, 0 cm = no pain to 10 cm = very severe, irresistible) at rest. The level of sedation was assessed using Ramsay scale (0, anxious or agitated or both, 6, no response to a light glabellar tap).<sup>17</sup> Furthermore, the patients were asked what they thought regarding this method and evaluated by 4 points of satisfaction scale 1. Totally dissatisfied 2. Moderately dissatisfied 3. Reasonably satisfied 4. Totally satisfied with pain relief. The patients were interrogated due to side effects such as nausea; vomiting, itching, hallucination, which was thought to be associated to drugs and the treatment, was also recorded. Additional analgesia (VAS >4) was available by maximum 75 mg daily diclofenac via intramuscular injection if requested by the patient. During the study, the same investigator held pain and sedation evaluations. Total analgesic consumption and bolus/demand ratio were determined at the same times via PCEA pump.

**Statistical analysis.** Differences in duration of surgery, amount of anesthetic solutions used, age, weight and height of patients were analyzed by one-way analysis of variance (ANOVA) (for normally distributed data) or Kruskal-Wallis one-way ANOVA on ranks (when data were not normally distributed). Side effect, nausea and vomiting, ASA physical status and satisfaction analysis were carried out with Chi-square test. Variance analyses of VAS, sedation, MAP and HR were carried out using repeated measurements of ANOVA test. Statistical analyses were performed using the SPSS® for Windows V10.0 (SPSS, Chicago, IL, USA). A value of  $p < 0.05$  was considered to be significant.

**Results.** There was not significant difference in demographic data, period of recovery stay and operation ( $p > 0.05$ ) as shown in **Table 1**. No significant difference was obtained in the comparison of HR,

**Table 1** - Demographic data (mean  $\pm$  SD).

Parameters	Group B (n =25)	Group N (n = 25)	Group F (n=25)
Age (year)	49.2 $\pm$ 8.5	45.5 $\pm$ 8.9	47 $\pm$ 7.8
Height (cm)	159.9 $\pm$ 5.4	162.8 $\pm$ 7.2	160.5 $\pm$ 5.8
Weight (kg)	71.8 $\pm$ 8.9	71 $\pm$ 7.5	69.8 $\pm$ 6.1
ASA I/II	16/9	18/7	16/9
Duration of surgery (min)	112.7 $\pm$ 26.4	114.7 $\pm$ 25.4	121.2 $\pm$ 26
PACU stay-period (min)	37.4 $\pm$ 11.5	34.5 $\pm$ 9.6	32.6 $\pm$ 5.3

ASA - American Society of Anesthesiologists, PACU - postanesthetic care unit

**Table 2** - Patient-controlled-epidural analgesia (PCEA) characteristics.

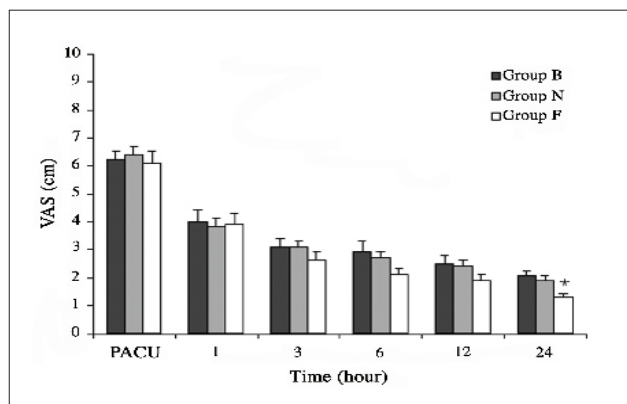
Parameters	Group B (n=25)	Group N (n=25)	Group F (n=25)
Analgesic consumption (mL)	143.7 $\pm$ 7.2	123.4 $\pm$ 6.2 <sup>a</sup>	106 $\pm$ 8.3 <sup>ab</sup>
PCEA ratio (bolus/demand)	44.9 $\pm$ 8.1	54.3 $\pm$ 11 <sup>a</sup>	63.7 $\pm$ 12.9 <sup>ab</sup>
Additional analgesic (%)	40	20	16

<sup>a</sup> -  $p < 0.05$ , as compared with Group B, <sup>b</sup> -  $p < 0.05$ , as compared with Group N

MAP, SpO<sub>2</sub> and RR values in the groups and between the groups by observing hemodynamic follow-up in recovery and during 24 hours ( $p > 0.05$ ). Lesser analgesics consumption ( $p < 0.05$ ) was found in Group F than the other groups after the end of 24 hours in the comparison of amount of analgesics. Total analgesic consumption was decreased in Group N than Group B ( $p < 0.05$ ). According to the comparison of PCA characteristics of groups; PCEA ratio (%) values (bolus/demand) were obtained significantly high in Group F rather than Group B at the end of 24 hours ( $p < 0.05$ ). Patient-controlled epidural analgesia ratio was also high in Group N rather than Group B (Table 2). Visual analogue scale of all groups was reduced since first hour of recovery. Visual analogue scale at 24 hours was found lower in Group F than other groups ( $p < 0.05$ ). At the end of this period, we obtained no difference between Group N and Group B. However, VAS values of all groups were  $< 3$  at the end of 24 hours (Figure 1). Significant decrease was seen in all groups according to the sedation data since one hour of recovery (from drowsiness to quiet and comfortable mood) ( $p < 0.05$ ). However, there was no difference between the groups ( $p > 0.05$ ). At the end of 24 hours, additional analgesic requirements of groups were observed (Table 2). No difference was obtained between the groups statistically. There was significant decrease in Group B according to the comparison of satisfaction scores of other groups at the end of 24 hours (score = 3) ( $p < 0.05$ ). No side-effects such as

hypotension, itching or hallucination were observed in any patient. However, nausea and vomiting were observed in different hours and no difference was obtained between the groups ( $p > 0.05$ ).

**Discussion.** Acute postoperative pain is a complicated, physiologic reaction due to disease and tissue injury. Patient-controlled-epidural analgesia is considered advantageous than other methods when compared due to better analgesic efficiency, patient's comfort and safety in studies.<sup>18,19</sup> Patient-controlled-epidural analgesia is reported to be superior to intravenous PCA and i.m. opioid administrations due to its faster recovery and shortened period of hospital stay.<sup>18,19</sup> Total analgesic demand and VAS values were seen lower with PCA in a study which compared infusions of postoperative PCA and continuous epidural infusion.<sup>20</sup> In order to provide good analgesia by diminishing stress response related to surgery without providing side effect, local anesthetics may be used in combination with adjuvants. Furthermore, multimodal or balanced analgesia have great role in postoperative pain management.<sup>21,22</sup> As a result, perfect postoperative analgesia can be obtained. It is reported that analgesia begins faster and lasts longer in patients receiving low doses of local anesthetics and opioids. Lesser motor block occurs rather than single use of these 2 drugs. Studies, which compared analgesic efficiency of opioid usage in PCA and addition of low dose opioid to local anesthetic bupivacaine in PCEA, reported that lesser opioid



**Figure 1** - Visual analog scale (VAS) values of groups (mean + SEM). \* $P < 0.05$  when compared with Group B and N. PACU - postanesthetic care unit

usage with PCEA and higher quality of analgesia with more patient pleasure.<sup>23</sup> In our study, the amount of analgesic usage and PCEA analgesic demand were seen lesser in fentanyl group than other groups as well as VAS values. Opioids are not very innocent agents even if they are used commonly in postoperative pain management. Side-effects of epidural opioids are itching, urinary retention and late respiratory depression. Cooper et al<sup>10</sup> have determined in their study of comparison; 0.1% bupivacaine and 4  $\mu\text{g mL}^{-1}$  fentanyl by PCEA with 0.05% bupivacaine and 2  $\mu\text{g mL}^{-1}$  fentanyl groups that the total amount of analgesic consumption and PCEA demand were lesser and the incidence of motor block was decreasing. However, the incidence of itching was too much in opioid group. Similar study also reported addictive analgesic effect with opioid addition to PCEA but also higher incidence in side-effects.<sup>24</sup> Side-effects related to opioid usage such as itching, hypotension, respiration depression were not observed at opioid doses used in our study. It is thought due to low dose of fentanyl usage and dose titration with PCEA method. Cholinergic system modulates pain perception and transmission by spinal mechanism.<sup>25-27</sup> Animal experiments have shown that intrathecal cholinesterase inhibitors increase acetylcholine in CSF and provide antinociception.<sup>11,27</sup> Intrathecal administration induces major gastrointestinal adverse effects precluding any clinical use,<sup>28,29</sup> whereas epidural injection of neostigmine causes postoperative pain relief without particular side effects.<sup>13,15</sup> Epidural neostigmine does not induce respiratory depression, motor impairment, or hypotension and hence matches the characteristics requested to induce selective analgesia. Neostigmine, an adjuvant, prolongs impact periods of local anesthetics and/

or opioids.<sup>14-16</sup> Omais et al,<sup>14</sup> compared epidural morphine (0.6 mg) versus morphine-neostigmine (60  $\mu\text{g}$ ) postoperatively for orthopedic surgery. They determined that first analgesic demand period was prolonged and additional analgesic demand lesser in neostigmine-morphine group. Nakayama et al,<sup>15</sup> studied bupivacaine with 5  $\mu\text{g kg}^{-1}$  and 10  $\mu\text{g kg}^{-1}$  doses of neostigmine in TAH operations and found out that first analgesic demand period prolonged. There were no significant differences between the groups due to VAS and side-effects. Kumar et al,<sup>16</sup> which added neostigmine to bupivacaine for unilateral inguinal herniotomy determined extended duration of postoperative pain relief. Neostigmine is supposed to prolong the analgesic effect of bupivacaine. There is no related side-effect in 4  $\mu\text{g kg}^{-1}$  neostigmine added to 0.125% bupivacaine. However, total analgesic consumption is found significantly lower in our study. The demand number applied in PCA is lower in neostigmine group than control group. There were no side-effects in postoperative PCA administrations with fentanyl and neostigmine groups added to local anesthetics in order to diminish analgesic amount and provide satisfaction of patients. Total analgesic usage and ratio of PCEA bolus/demand were found lower in fentanyl and neostigmine group. Visual analog scale values were significantly low in fentanyl group. As a result, we think that fentanyl and neostigmine with PCEA method which is considered to be effective for postoperative analgesia after abdominal operations; diminish analgesic consumption and increase quality of analgesia with safety.

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