ORIGINAL ARTICLE

Pre-emptive Analgesic and Haemodynamic Efficacy of Combined Spinal-Epidural Neostigmine Delivery

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ABSTRACT

Objective: To determine the effect of pre-emptive epidurally administered 4 or 8 mcg/kg neostigmine on analgesia, mean arterial pressure, heart rate and side effects in intra and postoperative period.

Study Design: Randomized, double blinded, controlled clinical trial.

Place and Duration of Study: Ankara Numune Training and Research Hospital, Turkey, from January to December 2008.

Methodology: Forty-five patients scheduled for lower extremity surgery were included in the study following the approval of the ethics committee and the patients. The study group was split into three groups and received combined spinal-epidural anaesthesia. Diluting with 10 ml normal saline, group N4 and group N8 were delivered 4 mcg/kg and 8 mcg/kg epidural neostigmine, respectively, whereas group SF received 10 ml epidural saline. Lidocaine (2%) at 1.2 mg/kg dose was preferred for spinal anaesthesia. Analgesic efficacy, time to first analgesic requirement, Visual Analog Scale, Fentanyl consumption in the postoperative patient-controlled epidural analgesia, and delivered/required number of boluses, were evaluated. Haemodynamic data and side effects were noted.

Results: Statistically, analgesic consumptions at 12 and 24 hours in the N8 group was lower than those in the SF group, the number of delivered boluses was lower in the N8 group compared with the SF and N4 groups, number of required boluses was lower in the N8 group than in the SF group. In terms of haemodynamics and side effects, no difference was found between the groups regarding the entire intraoperative and postoperative parameters.

Conclusion: Epidural Neostigmine administration at 8 mcg/kg was found to be a viable additional agent against analgesia, with the postoperative period depending on the dosage.

Key words: *Neostigmine. Epidural analgesia. Regional anaesthesia. Side effects.*

INTRODUCTION

Postoperative acute pain begins with surgical trauma and diminishes gradually with tissue healing. It is one of the most important problems of postoperative period. It may cause discomfort, depression, anxiety, and physiopathologic changes in the patients.[1]

One of the methods for pain management is pre-emptive analgesia.[2] A meta-analysis assessed the ability of pre-emptive analgesic interventions to attenuate post-operative pain scores, decrease supplemental post-operative analgesic requirements, and prolong the time to first rescue analgesia. It was found pre-emptive analgesia showed an overall beneficial effect in selected analgesic regimens that was most pronounced after epidural analgesia, local wound infiltrations, and systemic NSAID administration.[2] Narcotic agents are frequently preferred for analgesia. However, because of the well-known side effects of those agents such as respiratory depression, urinary retention, nausea-vomiting and pruritus, new agents are needed.[3]

Neostigmine is a cholinesterase inhibitor. Intrathecal neostigmine elevates the concentration of acetylcholine, which functions as an endogenous neurotransmitter in the cerebrospinal fluid, through inhibiting its degradation.[4] By stimulating the muscarinic receptors of acetylcholine across the spinal cord, particularly in the substantia gelatinosa (Lamina I-II), analgesia is established.[1,5] Neostigmine is an hydrophilic molecule like morphine, and when applied to the epidural space, requires a certain time for diffusing through dura mater and passing into the sub-arachnoid space.[1-12] Its analgesic effect has been shown to occur as a result of the blockage of Na^+ and K^+ flows in the anterior horn neurons of the spinal cord.[13]

Intrathecal neostigmine is noted to be efficient against acute and chronic pain in studies over humans.[3,4] In a series of clinical studies, intrathecal neostigmine doses. Analgesic effect is reported to occur between 25 -100 mcg dose range, cause side effects parallel to the dose elevation (bradycardia, increase in arterial blood pressure, nausea-vomiting, urinary retention), and have neurotoxic properties.[7,8]

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While, analgesic and its side effects have been shown for intrathecal practice by many studies, the studies concerning its epidural use are still ongoing.[3] Therefore, rationale and aim of the present study were to evaluate the analgesic properties and haemodynamic effects as well as side effects of pre-emptive epidural analgesia with 4 or 8 microgram neostigmine administration by combined spinal-epidural anaesthesia technique.

METHODOLOGY

The Ethical Committee of the Ankara Numune Training and Research Hospital approved the study protocol. The study was conducted at Ankara Numune Training and Research Hospital, Turkey, from January to December 2008. After giving informed consent, 45 patients, American Society of Anaesthesiologists status I, II and III, scheduled for minor orthopaedic procedures (lower extremity surgery) were included and randomized to one of three groups (n = 15 each) and prospectively studied using a placebo-controlled double-blind design to evaluate analgesia and adverse effects. Patients with a history of back surgery, mental retardation, infection at injection sites, coagulopathy, a history of opioid and chronic analgesic use, hypersensitivity to local anaesthetics or opioids, diabetes, peripheral neuropathy, coronary artery disease, advanced cardiac valve disease, an ejection fraction < 50% or advanced systemic diseases were excluded from the study.

The routine monitors were applied in the operating room including electrocardiograph, non-invasive blood pressure, and pulse oximeter (Datascope-Passport, 16377-AS, USA). Hydration consisted of 10 ml/kg lactate solution pre-operatively and 10 ml kg-1 h-1 after spinal anaesthesia.

A computer-generated random number table was used to provide randomization of patient allocation which was concealed in sealed envelopes and split into 3 groups (n=15). Group SF had lidocaine (1.2 mg/kg-intrathecal) + saline (epidural); group N4: had lidocaine (1.2 mg/kg-intrathecal) + neostigmine 4 mcg/kg (epidural)+ saline; and group N8 and lidocaine (1.2 mg/kg-intrathecal) + neostigmine 8 mcg/kg (epidural) + saline.

The patients, the investigators, and the research personnel involved in the data collection, as well as the personnel involved in the medical care of the patients, were all blinded to the assignment and study agents.

Combined spinal-epidural anaesthesia (CSEA) was instituted in the sitting position with a midline approach at the L_3 -L_4 or L_4- L_5 level in all subjects by the second author. The epidural space was located by the 16 gauge Thouhy needle using loss of resistance to air technique, and the dura was punctured by a 26 gauge spinal needle (Portex Ltd, Hythe, Kent; UK) that passed through the epidural needle. After observing the cerebrospinal fluid (CSF) flow, 2% lidocaine (1.2 mg/kg) was delivered to the intrathecal area and epidural catheter was placed. The patients were placed in supine position. Ten minutes after the intrathecal procedure, proper doses of neostigmine relative to the groups were delivered through the epidural catheter. After achieving a sensory block at T10 level, surgery was permitted.

At the end of the surgery, Patient-controlled anaesthesia device (PCA, Abbott Pain Management Provider), was connected to the epidural catheter and fentanyl (4 mcg/ml) was set up to have 2.5 ml/hour basal rate, 5 ml bolus dose, 15 minutes lock-out period, and 4-hour limit.

Intraoperative heart rate (HR) and mean arterial pressure (MAP) were recorded before the induction and at 5, 10, 15, 20, 30, 45, 60, 75, 90 minutes after the block. 0.5 mg intravenous (iv) atropine delivery was planned in cases where HR decreased below 60/minute, while planning 10 mg iv ephedrine administration when MAP dropped below 20% of the value before the block and oxygen mask application if SpO_2 was reduced below 90%. The number of patients having nausea (of any degree) or vomiting at any point intraoperatively was noted. Nausea greater than 2/10 (measured by the VAS pain score) or vomiting were treated with 10 mg intravenous metoclopramide.

By pin-prick test, the times when sensory block started and reached T10 dermatome were determined as well as revealing the level of sensory block, change in degree of block after the epidural 'top-up', and duration of anaesthesia.

The onset and level of motor block was evaluated based on the Bromage scale (0: no motor block, 1: unable to move the hip, 2: unable to move the hip and the knee, 3: unable to move the hip, knee, and the ankle).

Postoperative HR, and MAP values were recorded at 1, 2, 4, 6, 12, 24 hours. The time to first rescue analgesic (minute) was regarded to be the period between the moment of epidural neostigmine delivery and the time when patients took the first bolus.

Visual Analog Scale (VAS) was recorded by an assessment based on 0 - 10 at 1, 2, 4, 6, 12, 24 hours (0:no pain through 10:very severe pain). Diclofenac at 75 mg dose intramuscular (im) was used in cases where VAS raised above 4. Total fentanyl consumption in 24 hours was recorded from the PCA device. The number of boluses delivered for 24 hours after the disconnection of the PCA device as well as the number of required (including the bolus requirements that have not been used due to overlap with the lockout period) boluses were recorded.

It was hypothesized that 4 mcg/kg or 8 mcg/kg neostigmine would increase the time to first rescue analgesic by 100% when compared to control group. If the standard deviation for this prospective power

analysis was estimated at 40% and value of 0.05, these assumptions would require 5 patients in each group to see a 100% increase in the time of the first rescue analgesic. To further increase the power, it was elected to observe 15 patients in each group.

The data were analysed using Statistical Package for Social Sciences (SPSS for Windows, release 11.0). Variables were tested for normal distribution. Groups were compared for demographic data (age, weight, and height) by one-way analysis of variance. Incidence of adverse events, gender were compared among groups by chi-square analysis corrected for multiple tests. Kruskall-Wallis H test was used to compare maximum sensorial block level between groups. The time to first rescue analgesics was compared among groups by one-way analysis of variance. VAS scores were compared among groups by two-way analysis of variance for repeated measures. Variables were expressed as mean (SD), median (range) or number of patients (n). Bonferroni test was used to determine the origin of difference in the variance analysis performed within the repeated measurements. Tukey Honest analysis was applied to correct p-values. $P < 0.05$ was considered significant.

RESULTS

There was no statistically significant difference between the groups with regard to demographic data, duration of the anaesthesia and duration of surgery ($p > 0.05$, Table I). In terms of number of boluses required and delivered, there was a statistically significant difference between the three groups ($p < 0.01$). This value was found to be significantly low in the N8 group as a result of the analysis of the mean values (Table I). No significant difference was found across the groups relative to sensory block onset time and motor block onset time, and time to reach T_{10} dermatome (Table II). Motor block level was Bromage grade 3 in all the groups except one patient in each group. Following epidural top-up, there was no significant difference across the groups with regard to sensory block increases and maximum sensorial block level ($p > 0.05$, Table II). The maximal sensory block achieved in group SF, group N4 and group N8 was similar (median T4 [min-max] T3 to T6 and median T5 [min-max] T3 to T7, and median T5 [min-max] T3 to T6 respectively, $p = 0.32$).

In terms of intraoperative HR changes, HRs at 30, 45, 60 minutes were found to be significantly low in the N8 group ($p < 0.05$). No statistically significant difference was determined in terms of postoperative HR ($p > 0.05$, Table III). There was no difference statistically between the groups relative to the intraoperative and post-operative MAP ($p > 0.05$, Table IV). No difference was determined between the intraoperative SpO_2 ($p > 0.05$).

There was no significant difference between the intra-operative ephedrine, atropine, metoclopramide uses in terms of percentages and frequencies ($p > 0.05$). Twelve patients in the SF, 8 patients in the N4, 10 patients in the N8 used 10 mg ephedrine. Three patients in the SF, 4 patients in the N4, 5 patients in the N8 used 0.5 mg

Table I: Demographic characteristics.†

Variables	Group SF (n=15)	Group N4 (n=15)	Group N8 (n=15)	p-value
Gender (F/M)	6/9	5/10	5/10	0.900
Age (years)	37.9±11.6	34.5±12.2	40.7±10.3	0.330
Weight (kg)	73.8±10.8	74.5±11.0	75.5±12.0	0.920
Height (cm)	171.0±8.2	173.6±6.6	169.9±8.9	0.440
ASA Class (I-II-III)	3-11-1	7-7-1	3-11-1	No test
Duration of anaesthesia (min)	95.67±4.58	98.00±4.55	98.00±4.93	0.320
Duration of surgery (min)	72.0±15.9	71.3±14.0	74.6±10.9	0.780
Number of boluses delivered	11.80±4.11	10.93±3.26	7.53±3.11	0.005**
Number of boluses required	14.20±5.58	12.07±4.06	8.73±4.17	0.005**

***: P < 0.01*
† Values are means ± SD or number of patients (n)
No significant differences between the three groups.
Groups were compared for demographic data (age, weight, and height) by one-way analysis of variance. Incidence of adverse events, gender were compared among groups by chi-square analysis corrected for multiple tests.

Table II: Intra-operative and postoperative block characteristics.†

Variables	Group SF (n=15)	Group N4 (n=15)	Group N8 (n=15)	p-value
Sensory block onset time (min)	2.67±0.61	3.13±0.74	3.13±0.74	0.120
Motor block onset time (min)	3.67±0.61	4.06±0.97	4.13±0.64	0.200
Time to reach T10 dermatome (min)	4.33±0.61	4.66±0.90	4.60±0.83	0.480
Maximum sensorial block level	T4 (3-6)	T5 (3-7)	T5 (3-6)	0.320
Time to first rescue analgesic (min)	111.93±26.68	109.86±21.49	143.73±85.10	0.150

†Values are the median(range) or means ±SD
No significant differences between the three groups.
Kruskall-Wallis H test was used to compare block characteristics between groups.
The time to first rescue analgesics was compared among groups by one-way analysis of variance.

Table III: Intraoperative and postoperative heart rate changes.

Time	Group SF (n=15)	Group N4 (n=15)	Group N8 (n=15)	p-value
Before block	82.51±14.83	90.07±17.28	85.85±10.78	0.760
5 min.	84.07±16.29	86.26±18.10	82.73±14.49	0.830
10 min.	76.13±17.28	78.73±20.13	76.40±17.80	0.910
15 min.	76.67±12.86	80.67±18.50	73.33±11.38	0.390
20 min.	76.33±11.30	78.47±17.78	69.67±8.02	0.160
30 min.	79.93±12.78	84.33±17.18	69.80±7.73	0.010*
45 min.	83.06±14.31	80.80±13.71	69.86±10.03	0.020*
60 min.	84.78±15.77	79.33±11.62	72.93±8.28	0.040*
75 min.	87.83±17.97	84.36±13.30	77.28±8.87	0.140
90 min.	90.86±21.94	88.29±16.30	72.00±8.17	0.090
Postoperative				
60 min.	84.87±13.30	79.20±9.87	83.46±6.57	0.300
120 min.	84.00±12.90	79.67±9.12	81.73±6.76	0.490
240 min.	83.40±12.07	80.87±9.10	82.53±6.57	0.760
360 min.	83.87±10.84	80.93±8.75	81.67±5.97	0.630
720 min.	82.00±8.78	80.13±7.85	80.67±6.74	0.790
1440 min.	77.60±5.76	79.07±7.43	78.93±5.85	0.780

p < 0.05; † Values are means ± SD.
No statistically significant difference was determined in terms of postoperative HR values.

atropine. Three patients in the SF, 1 patients in the N4, 3 patients in the N8 used 10 mg metoclopramide in the operation.

Time to first rescue analgesic was found to be approximately 30 minutes longer in N8 group than the other two groups (Table II). No patient needed diclofenac in any group. Regarding VAS analysis, no statistically significant difference was determined ($p > 0.05$, Table V). Postoperative fentanyl consumption values at 12 and 24 hours were significantly low in the N8 group (Table V). There was no difference with regard to postoperative nausea-vomiting. Among N4 group, one patient had nausea upto postoperative five hours along side vomiting, whereas another patient demonstrated nausea till 2.5 hours postoperative. In the N8 group, one patient complained of nausea at postoperative 12 hours, but none in the SF group. There was no difference with regard to postoperative pruritus. Pruritus demonstrated 2, 2 and 1 patient in the SF, N4 and N8 group respectively.

Table IV: Intra-operative and postoperative mean arterial blood pressure changes .

Time	Group SF (n=15)	Group N4 (n=15)	Group N8 (n=15)	p-value
Before block	92.00±11.24	95.20±9.13	94.20±1.05	0.690
5 min.	83.07±13.64	88.07±7.02	86.13±14.35	0.520
10 min	75.33±10.85	78.26±10.25	80.80±17.01	0.520
15 min.	85.80±14.97	82.33±8.11	81.00±10.13	0.500
20 min.	84.80±12.12	83.13±10.87	81.53±8.50	0.700
30 min.	84.73±7.91	83.67±8.10	81.47±10.56	0.590
45 min.	86.87±9.86	84.67±13.94	81.80±10.15	0.480
60 min.	88.50±10.14	84.80±12.14	84.87±10.32	0.580
75 min.	91.50±9.44	86.00±13.20	89.00±9.73	0.480
90 min.	87.14±16.86	89.43±7.67	92.00±8.77	0.740
Postoperative				
60 min.	92.20±6.89	90.67±6.33	96.27±9.91	0.140
120 min.	93.07±7.00	89.93±7.48	92.67±5.88	0.390
240 min.	89.60±7.85	90.27±7.86	94.07±8.59	0.270
360 min.	92.87±7.99	89.53±4.73	91.20±9.93	0.510
720 min.	89.00±6.10	82.06±20.45	90.06±8.18	0.720
1440 min.	86.00±4.04	88.67±5.73	88.93±6.60	0.290

Table V: Postoperative VAS analysis and Fentanyl consumption.

	Group SF (n=15)	Group N4 (n=15)	Group N8 (n=15)	p-value
VAS				
1 hour	2.33±0.82	2.20±1.20	1.87±1.25	0.490
2 hour	2.60±1.12	2.27±1.03	1.73±0.80	0.060
4 hour	2.53±1.50	2.26±0.88	1.87±0.92	0.280
6 hour	2.33±1.18	2.07±1.10	1.80±0.94	0.400
12 hour	2.00±0.85	1.87±0.92	1.33±0.82	0.090
24 hour	0.53±0.91	0.53±0.51	0.13±0.35	0.150
Fentanyl consumption				
1 hour	37.30±14.40	30.78±11.60	26.86±12.47	0.090
2 hour	62.96±21.13	48.64±12.47	51.23±16.16	0.060
4 hour	114.23±34.78	93.32±21.44	93.33±28.99	0.080
6 hour	145.82±36.75	136.73±30.79	122.43±25.74	0.130
12 hour	261.75±47.47	240.94±50.12	209.74±37.45	0.011*
24 hour	470.20±80.22	453.13±63.54	386.42±60.94	0.004**

** $p < 0.05$ ** $p < 0.01$*
(VAS scores were compared among group by two-way analysis of variance for repeated measures)

DISCUSSION

This clinical research has shown analgesic consumptions at 12 and 24 hours in the N8 group was lower than those in the SF group, the number of delivered boluses was lower in the N8 group compared with the SF and N4 groups, number of required boluses was lower in the N8 group than in the SF group. In terms of haemodynamics and side effects, no difference was found between the groups regarding the entire intraoperative and postoperative parameters.

Studies that evaluate the analgesic effect of neostigmine report prolonging of the time to first analgesic requirement.[7,12-16] In the present study, regarding the time to first analgesic requirement, there was statistically significant difference across the groups. Based on the mean values (SF=111.93 min, N4=109.86 min, N8=143.73 min), the time to first analgesic requirement was determined to be prolonged around 30 minutes in the N8 group compared with the other two groups. These results may be due to preferring short-acting local anaesthesia for spinal anaesthesia, absence of local anaesthesia practice in combination with neostigmine, and short length of our operations.

Lauretti *et al.* conducted two studies and found significantly low VAS values in the neostigmine groups.[10,12] On the other hand, Nakayama *et al.* found no difference between the groups regarding VAS results.[15] In the present study, no statistically significant difference was found between the three groups relative to the postoperative VAS values. We believe, further studies should be performed on this subject.

Neostigmine has been found to reduce the analgesic consumption when applied via intrathecal or epidural routes, whereas morphine consumption and the number of diclofenac needed in the postoperative period have been reported to exhibit a decrease.[14] In a study including patient-controlled anaesthesia through intrathecal neostigmine and intravenous morphine, analgesia consumption was reported to fall after 6 hours. In the same study, it was noted that activation of the noradrenergic/cholinergic anti-nociceptive system might be effective and that neostigmine might generate a selective analgesia that increases in time in the postoperative period.[17] Analgesic effect of the epidural neostigmine is reported to increase when local anaesthetic is delivered.[12,13] Selective analgesic property of neostigmine may be the underlying reason for analgesic efficacy at higher doses. In the current study, the decrease in analgesic consumption started after 12 hours and selective analgesic property of neostigmine was thought to be the underlying reason.

Lauretti *et al.* delivered 1, 2, 4 mcg/kg neostigmine in combination with 85 mg lidocaine (1%) into the epidural space via CSEA technique and determined similar intraoperative heart rates in all the three groups.[12] Bradycardia was detected only in one patient of the 1 mcg/kg group and in another patient of the 4 mcg/kg group; these cases were treated with 0.25-0.50 mg atropine. During the postoperative period, none of the groups demonstrated a change in the heart rate or a bradycardia.[12]

In the present study, there was a statistically significant difference between the 4 mcg/kg and SF groups with regard to heart rate. The difference in the 8 mcg/kg group relative to the heart rate was probably due to delivery of high-dose neostigmine. Heart rate may also fall because of the passage of the drug by vascular absorption from the epidural space to the systemic circulation. Moreover, it may diffuse from the dura mater into the CSF and indirectly stimulate the muscarinic receptors in the nucleus tractus solitarius by cephalic distribution. Probably the amount of neostigmine passing into the systemic circulation from the vascular structures in the epidural space is not much, however, bradycardia may occur even at very low doses via parenteral delivery.[4]

The difference with regard to intraoperative atropine may be originating from the method difference. Lauretti *et al.*[12] recognized the lower limit for atropine delivery as 50/minute.[11] However, it was defined the same limit as 60/minute. While there are studies which suggest that neostigmine, a cholinesterase inhibitor, indirectly stimulates spinal pre-ganglionic sympathetic neurons in intrathecal administrations.[8,18,19] There are studies showing no statistical difference in terms of blood pressure and ephedrine consumption.[7,12,14]

In the current study, no statistically significant difference was found with regard to intraoperative and postoperative mean arterial blood pressure changes and intraoperative ephedrine consumption($p > 0.05$).

Neostigmine can lead to high blood pressures only at high doses.[1-3] The difference between results of intrathecal neostigmine studies and the present differ due to the fact that the amount of delivered epidural doses that passed into the systemic circulation via epidural space by vascular absorption or passed into the CSF through dura mater, were at levels that would not effect the arterial blood pressure.

Neostigmine stimulates muscarinic receptors in the bronchial smooth muscles and leads to bronchospasm while increasing the number of mucosal glands in the respiratory tract and enhancing the resistance of airways.[20] In intrathecal neostigmine studies, except at very high doses (eg. 750 mcg), no change has been detected in oxyhaemoglobin saturation and 'end-tidal carbondioxide' levels.[7,8,9] At very high doses, a decrease in the 'end-tidal carbondioxide' levels has been found without any changes in the oxyhaemoglobin saturation.[8] In the present study, there was no difference between the groups in terms of intraoperative oxyhaemoglobin saturation changes.

Most commonly observed side effect in intrathecal neostigmine administrations, is nausea-vomiting.[17] Nausea-vomiting have been shown to occur in a dose-related fashion.[5,8,17] Nausea-vomiting associated with epidural neostigmine administration was thought to be arising due to lower amount of neostigmine diffusion from dura and absence of cephalic distribution. Nausea-vomiting is seen less frequently in epidural neostigmine studies.[12,14] In the current study, there was no difference between the number of cases in which we were required to deliver drugs because of nausea-vomiting. Moreover, we could not differentiate whether nausea-vomiting were occurring due to spinal anaesthesia or not. In the postoperative period, nausea-vomiting was observed in 2 patients of N4 group and 1 patient of N8 group. These results were consistent with those of other epidural neostigmine results.

Pruritus has been observed only in the study of Krukowski among the individuals subjected to morphine. In the present study, pruritus was localized to the nose and face, associating it with fentanyl used in patient-controlled epidural analgesia.[17]

Intrathecal neostigmine on volunteers, revealed neurologic side effects such as weakening in the deep tendon reflexes, disruption in motor function, sedation, anxiety and they were found to have a correlation with dose increases. These side effects were believed to be associated with the central cholinergic excitation.[8] Studies conducted with epidural neostigmine showed no side effect other than those.[12,14,18] None of those side effects were found in this study as well.

CONCLUSION

It is concluded that pre-emptive 8 mcg/kg epidural neostigmine reduced analgesic consumption with low frequency of adverse effects.

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