ORIGINAL ARTICLE

A comparison of post-operative analgesic and hemodynamic effects of extradural neostigmine plus fentanyl with fentanyl alone in patients of hysterectomy

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ABSTRACT:

Objective: To study the comparative analgesic and haemodynamic effects of fentanyl with a combination of neostigmine plus fentanyl administered epidurally for post-operative pain in patients undergoing hysterectomy.

Study Design: This is an interventional, randomized, controlled study leading to therapeutic trial of a combination of drugs.

Place & Duration: The study was conducted at High Dependency Unit (HDU), Nishtar Hospital Multan, Pakistan. The study was completed in six months period from June to December 2004.

Patients & Methods: One hundred female patients belonging to age range 40 60 years, of ASA 1 and 2, undergoing elective abdominal hysterectomy, were included in this study. They were randomly divided into two groups by the consultant anaesthetist. Patients having any clinical or biochemical evidence of any systemic disease were excluded from the study.

The procedure was explained to the patients and informed consent was obtained. All the patients were examined an evening before the operation. A lumber epidural catheter was passed before induction of general anesthesia. From immediate postoperative period till 20 hours, patients were given fentanyl alone in group A and fentanyl plus neostigmine in group B by epidural infusion. While assessing the intensity of pain relief in both the groups, the effects on hemodynamics were also recorded.

Results: Significant reduction in the intensity of pain was noted in the neostigmine plus fentanyl group. Moreover lower values of mean arterial pressure were recorded in this group, while significantly slower heart rates were found in the 4thto 7th hours of postoperative period.

Conclusion: Epidurally administered neostigmine along with fentanyl gives better pain (qualitative) relief than fentanyl alone. Lower values of mean arterial pressure and slower heart rates at 4, 5, 6 and 7 hrs of infusion were seen.

Key Words: Postoperative analgesia; Epidural; Fentanyl; Neostigmine.

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INTRODUCTION:

Pain is a major concern in the postoperative period. Postoperative pain relief, however, has been sadly ignored and this aspect has been frequently highlighted in the medical literature by the eminent members of the medical profession. A variety of drugs has been used singly or in combination for postoperative pain relief either parenterally or by regional blocks. Parenteral opioids are most often used either intermittently or by continuous infusion. These can lead to numerous side effects such as nausea ,vomiting, sedation and respiratory depression. Epidural analgesia offers excellent analgesia following surgery[1]. Pharmacology of epidural opioids, local anesthetics and combination therapy is well documented. Local anesthetic agents alone have been used through epidural route but are associated with hypotension, motor block and can result in systemic toxicity.

The discovery of opioid receptors in spinal cord has led to an alternate therapy, e.g., epidural and intrathecal administration of narcotics. This technique produces prolonged segmental analgesia without somatic, sensory or sympathetic blockade[2]. However side effects have been reported, the most serious being respiratory depression with the use of opiates. For the last one decade [2] adrenergic agonists like clonidine along with narcotics is being used with promising results. Recently, acetyl cholinesterase inhibitors have been used for augmenting analgesic effects of opioids and local anesthetics. The cholinergic system is thought to modulate pain perception and transmission by a spinal mechanism, and intrathecal administration of cholinesterase inhibitors provides antinocioception by increasing acetylcholine in the cerebrospinal fluid (CSF). Lauretti and Lim demonstrated the analgesic effects of intrathecal injection of neostigmine in volunteers and patients with acute postoperative pain[3]. However, there have been scanty evidence on the effectiveness of epidural neostigmine for postoperative analgesia[4].

In the current study, we evaluated the effects of epidurally administered neostigmine together with fentanyl, on the degree of postoperative pain alleviation and on haemodynamics in patients undergoing transabdominal hysterectomy with general anaesthesia.

PURPOSE OF STUDY:

To evaluate the effects of epidurally administered neostigmine together with fentanyl, on the degree of postoperative pain alleviation and on the hemodynamics as compared to the effects of epidurally administered fentanyl.Methodology:

This was an interventional (analytical) study leading to therapeutic trial of drugs. The study was conducted at HDU (High Dependency Unit) Nishtar Hospital Multan. Following the approval of ethical committee written, informed consent was taken from 100 adult female patients to participate in the study. These patients were scheduled for routine transabdominal hysterectomy (TAH). The patients belonging to ASA I or II status were randomly allocated to one of two groups i.e. Group A, those who received epidural fentanyl alone and Group B, who received a combination of neostigmine and fentanyl. The patients were instructed at the time of recruitment regarding the evaluation of postoperative pain intensity using the visual analogue scores (VAS). The VAS consisted of zero to 10, zero being no pain and 10 the worst possible pain. All the patients were examined an evening before the operation. The patients with a history of allergy to local anesthetics were excluded from the study, as was any patient showing clinical or biochemical evidence of renal, cardiac or GIT system involvement.

All the patients were premedicated with tablet midazolam 7.5mg orally, 1.5 hrs before arrival in the operating room (OR). All patients received 500ml of Hartmann's solution before induction of anaesthesia. The patients were monitored as per routine i.e. ECG,

Table 1: Comparative Pain Scores at rest and while coughing in both groups

Time (hours)	Pain at rest (VAS-P)					Pain while coughing (VAS-C)				
	Group A		Group B		p	Group A		Group B		p
	Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.	
0	0.25	0.57	6.25	0.54	<0.0001	0.25	0.57	6.25	0.20	<0.0001
3	1.5	0.50	0.5	0.05		3.0	0.50	0.25	0.25	
6	3.0	0.51	0.75	0.51		4.0	0.72	0.5	0.50	
9	3.5	0.52	1.5	0.54		4.5	0.53	2.5	0.50	
20	3.5	0.57	1.5	0.53		5.0	0.50	2.5	0.50	

oxygen saturation (SpO2), non invasive blood pressure (NIBP), fraction of inhaled oxygen (FiO2) and end tidal carbon dioxide (EtCO2). Although operations were performed under general anesthesia/narcotic technique but epidural catheter was passed before induction through an 18 gauge tuohy needle using the loss of resistance technique at either L2-3 or L3-4 interspace and tested with 2ml. Anaesthesia was induced using fentanyl 1-2 microgram per kg and propofol 2-3 mg/kg; and muscle relaxation was facilitated using vecuronium. Following tracheal tube placement and confirmation of correct position, anaesthesia was maintained using isoflurane in nitrous oxide and oxygen. The patients were randomly allocated to group A or B by the consultant anaesthetist and were given drugs epidurally as planned below.

At the time of wound closure the patients in group A were given fentanyl 100µg in 15 ml in the epidural space, while the patients in the group B were given fentanyl 100µg & Neostigmine 100µg in 15 ml of saline in the epidural space. Then an epidural infusion of fentanyl 2µg/ml in normal saline was started at the rate of 4ml/hour in group A, and fentanyl 2µg/ml + neostigmine 2.5µg/ml in normal saline at the rate of 4ml/hour was given in group B.

Pain intensity at rest (VAS-R) and during coughing (VAS-C) was evaluated using 10cm VAS after tracheal extubation by the consultant anaesthetist, and 3, 6, 9 and 20 hours after completion of operation by the postgraduate registrar on duty in the HDU. All the patients were kept under observation in the HDU for close monitoring and proper record. Mean arterial blood pressure was measured automatically using a noninvasive oscillometric method and heart rate was read from ECG monitor. Performa showing hourly record of BP, pulse and pain scoring on cough was filled by the staff of HDU. All data are presented as means + SD. Demographic data (age, height and weight of the patient) are presented and results are analyzed using SPSS-8 package. Since all variables in study were numeric, t-test was used to compare means and standard deviations. A difference was considered statistically significant if the p-value was found to be 0.05 or below.

RESULTS

Data from 100 patients, ASA-I & II, included in the study were analyzed. As mentioned earlier there were 50 patients in each group. Both groups had had similar patient profiles. The mean age in group A was 48+8 years, while in group B the mean age was 50+7

Table 2: Comparative variability in the heart rate and mean arterial blood pressure in both groups

Time (hours)	Heart rate (beats per minute)					Mean Arterial Pressure (mm Hg)				
	Group A		Group B		p	Group A		Group B		p
	Mean	S.D.	Mean	S.D.		Mean	S.D.	Mean	S.D.	
0	80	5	80	7	1.00	95	10	96	10.5	0.63
3	75	5	65	6	<0.0001	90	12	80	11.5	<0.0001
6	68	5	54	5		98	10.5	70	5.5	
9	73	7	56	7		100	8	72	5.8	
20	70	6	60	6		108	8.5	75	10	

years. The difference in both groups was not significant statistically (p=0.19). Similarly the mean weight in group A was 60 kg (S.D. = 9.4 kg) and in group B was 62 kg (S.D. = 10.2 kg). In group A, 35 (66.6%) patients were in ASA Class I while 15 patients (33.3%) were in class II. In group B 22 (46.6%) patients were in class I and 28 (53.4%) were in class II.

Neostigmine potentiated the analgesic effectiveness of fentanyl administered into extradural space which manifested itself with lower scores of pain intensity felt during coughing attempts, 3, 6, 9 and 20 hours after completion of operation (P<0.0001) (Table 3,4). In group B, lower values of mean arterial pressure (P<0.0001) were observed from 3-20 hours after completion of operation while the heart rates were also significantly slower at 3, 6, 9 and 20 hours after extubation. Severe hypotension (mean arterial pressure <60 mmHg) or bradycardia (heart rate <50 beats per minute) were not observed in any patient. Arterial oxygen saturation (SpO2) was always within the clinically acceptable range of >95%

DISCUSSION:

Intrathecal administration of the cholinesterase inhibitors, edrophonium, physiostigmine and neostigmine has been shown to produce analgesia in animal and human studies. This action is blocked by muscarinic antagonists, indicating that spinal muscarinic receptors are involved in their analgesic properties. The muscarnic receptors are present in the superficial laminae of the dorsal gray matter of the spinal cord. In recent clinical studies, intrathecal neostigmine in doses ranging from 10μg to 200μg, induced analgesia in patients undergoing vaginal hysterectomy, cesarean section, and orthopedic surgery[5]. In our study it was found that the addition of neostigmine significantly prolonged analgesia produced by epidural fentanyl. Lauretti et al showed that 1-4μg/kg of intrathecal neostigmine produced a dose independent analgesic effect[6]. In another study Nakayama et al have shown that large dose neostigmine 10μg/kg as compared to 5μg/kg produced analgesia[7].

In our study we assessed analgesic effect of fentanyl, as compared to fentanyl plus neostigmine given by epidural infusion. The total amount of neostigmine required by one patient in 20hrs was 400-500 μg i.e. roughly 6.5-7.5μg/kg/20hours. The calculated dose/hr was 0.3-0.4μg/kg/hr. This dose is much less as compared to Nakayama study, and provided satisfactory analgesia. It has been suggested that analgesia induced by intrathecal cholinesterase inhibitors depends on the degree of tonic release of acetylcholine in the spinal cord. Therefore, one could expect that the analgesic potency of intrathecal neostigmine would be influenced by the nature of the surgery, being greater after more extensive and painful procedures. It needs to be further studied. The nausea and vomiting are the most common and troublesome side effects of intrathecal neostigmine. This fact is likely to be due to rostral migration of neostigmine in the CSF[8]. In the study of Lauretti et al the postoperative VAS of nausea in the control group and neostigmine treated groups were similar. This result is consistent with our observations also.

We could not rule out the possibility of the association of general anaesthesia in our study with the absence of adverse effects, nausea and vomiting postoperatively. No effects on hemodynamics have been reported when neostigmine is given intrathecally or in epidural space[9]. In a recent study done at Hamdard Medical University Hospital, Karachi in collaboration of Department of Anesthesiology and Surgical Unit, DMC and Civil Hospital Karachi, neostigmine was given intrathecally in a dose of 15μg with hyperbaric (0.75%) bupivacaine[10]. This group was compared with control group to which hyperbaric bupivacaine was given with normal saline. The study was done to evaluate the analgesic effectiveness of neostigmine addition along with the side effect. The study revealed nausea and vomiting in clinical and statistically significant number of patients

which corroborate with past studies. This adverse effect is probably caused by cephalad migration of neostigmine to brainstem. Motor block was greatly prolonged in neostigmine group of the study. The duration of postoperative analgesia was significantly prolonged in this group.

In our study there had been a drop in BP and HR (Tables 1,2) in 3rd, 6th , 9th and 20th hours of infusion. In both the groups there was no effect on respiratory rate, and SpO2 remained consistently within normal range.

Our study is different and unique as compared to the studies reported in the literature. Most of the studies have reported effect of intrathecal neostigmine but in our study the epidural route was used. No study has been carried out up till now to compare the effectiveness of fentanyl plus neostigmine administered epidurally and continued in an infusion after the bolus dose.

CONCLUSION:

Neostigmine administered with fentanyl in the extradural space in the postoperative period, as continuous epidural analgesia gives better pain relief than fentanyl alone. The requirement of total amount of fentanyl per hour is reduced. The combination significantly lowers the heart rate particularly in 4th to 7th hrs of infusion, and lower values of mean arterial pressure are seen in this period.

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