

OPIOID INDUCED HYPERALGESIA: EPIDURAL FENTANYL FOLLOWED BY INTRAVENOUS DEXMEDETOMIDINE INFUSION VERSUS INTRAVENOUS PARACETAMOL– A COMPARATIVE STUDY

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ABSTRACT

BACKGROUND

Opioid induced hyperalgesia (OIH) is a state of nociceptive sensitisation caused by exposure to opioids probably due to paradoxical sensitization to painful stimuli.

The aim of the study is to study the presence of OIH in acute pain management and to compare the ability of intravenous paracetamol and intravenous dexmedetomidine in allaying OIH in patients receiving epidural Fentanyl following total abdominal hysterectomy.

MATERIALS AND METHODS

The study was an observational study including sixty patients divided into three groups. All three groups received Epidural Fentanyl as infusion at the rate of 10-15 mcg/hr with intravenous fentanyl bolus as rescue analgesic on Post-Operative Day 1(POD), Group F- On POD 2 received Inj. Fentanyl 50 mcg iv 8th hourly and SOS. Group P- On POD 2 received Inj. Paracetamol 1 gm iv and inj fentanyl SOS. Group D- On POD 2 received Inj. Dexmedetomidine iv as infusion @ 0.02mcg/kg/hr and Inj. Fentanyl SOS. Pain was assessed using visual analogue score (VAS) at 4,12,24,48 hrs and at dressing change on POD 2.

RESULTS

No statistically significant difference in Pain scores at 4,12,24,48 hrs. Statistically significant difference in pain scores at dressing change was noted in group F ,but no significant difference in VAS between Group P and D.{VAS at dressing change: Group F=4.20; Group P=3.05; Group D=2.70}

CONCLUSION

PAIN sensed by patients during dressing change was significantly more in patients receiving opioids alone as opposed to a combination of opioids with paracetamol and dexmedetomidine.

KEYWORDS

Fentanyl, Opioid Induced Hyperalgesia, Hysterectomy, Epidural, Analgesia.

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BACKGROUND

Opioid-induced hyperalgesia (OIH) is most broadly defined as a state of nociceptive sensitization caused by exposure to opioids. The state is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain may actually become more sensitive to certain painful stimuli. The type of pain experienced may or may not be different from the original underlying painful condition. Although the precise molecular mechanism is not yet understood, it is generally thought to result from neuroplastic changes in the peripheral and central nervous systems that lead to sensitization of pronociceptive pathways. OIH seems to be a distinct, definable, and

characteristic phenomenon that may explain loss of opioid efficacy in some cases. Clinicians should suspect expression of OIH when opioid treatment effect seems to wane in the absence of disease progression, particularly if found in the context of unexplained pain reports or diffuse allodynia unassociated with the pain as previously observed.

This study aimed to detect the presence of opioid induced hyperalgesia in an acute setting.

Abdominal hysterectomy is associated with moderate-to-severe postoperative pain.¹ Traditional methods for postoperative pain management include opioids administered systemically using patient-controlled i.v. analgesia (PCA), or neuroaxially via epidural or spinal injections. However, pain relief, specifically on movement, is not always adequately controlled when using PCA, despite moderate–large doses of morphine. This is associated with side-effects such as postoperative nausea and vomiting (PONV), tiredness, pruritus, headache, and constipation.² Therefore, epidural or intrathecal analgesia may be considered by some to be the gold standard for pain management after abdominal surgery, and leads to enhanced and prolonged postoperative analgesia.

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Continuous epidural fentanyl infusion, PCEA, or both provide excellent analgesia and overcome the limitations to the duration of action associated with epidural bolus administration. Although analgesia is excellent at rest, pain scores increase with movement and coughing.^{3,4}

MATERIALS AND METHODS

After obtaining Local Ethics and Research Committee approval and written informed consent from patients an observational study was performed.

Sixty patients of American Society of Anaesthesiologists Physical Status Class I and II, undergoing total abdominal hysterectomy were enrolled in the study. Inclusion criteria included Patients between 30 -50 years of age undergoing total abdominal hysterectomy during 6 months from 1st April 2016 to 30th September, under Combined Spinal Epidural Block at Sree Gokulam Medical College. Patients with known drug allergy to the study drugs were excluded from the study.

A written informed consent was obtained from the patients. Patient was kept nil per oral for 8 hours preoperatively. At least one 18G or larger cannula inserted on a forearm vein. All 3 groups were premedicated with Midazolam 0.02 mg/kg iv and Ondansetron 0.15 mg/kg iv. ECG, Pulse oximetry & Non Invasive Blood Pressure monitoring done. Combined Spinal Epidural Block under strict aseptic precautions was given to the patient. Intra operative epidural top up using 0.5% bupivacaine given to all 3 groups. Intraoperative monitoring done and patients shifted uneventfully to post anaesthesia care unit (PACU).

Based on their postoperative analgesia plans the patients were divided into 3 groups

Group F: Fentanyl only.

Post operatively given Epidural Fentanyl as infusion @ 10- 15 mcg/hr alone on Postoperative Day-1. On Postoperative Day 2 analgesia maintained by Inj. Fentanyl 50 mcg iv 8th hourly and as rescue analgesic.

Patients pain was assessed using Visual analogue score (VAS) {Score of 1 to 10; 1 being no pain and 10 being worst imaginable pain. Scores of four or more treated with rescue analgesic.}. VAS at 4, 12, 24 and 48 hrs was noted.

Dressing change after 2nd postoperative day was taken as the stimulus for hyperalgesia Hence VAS at dressing change noted.

GROUP P– Fentanyl followed by Paracetamol.

Patients in this group received Epidural Fentanyl as infusion @ 10-15 mcg/hr alone on Postoperative Day 1 and On Postoperative Day 2 analgesia maintained by Inj. Paracetamol 1 gm iv 8th hourly With Inj. Fentanyl 50 mcg as rescue analgesic. VAS for pain noted at the same times as group F

GROUP D- Fentanyl followed by Dexmedetomidine

Patients in this group received Epidural Fentanyl as infusion @ 10- 15 mcg/hr alone on Postoperative Day 1 and On Postoperative Day 2 analgesia was maintained by Inj. Dexmedetomidine iv as infusion @.02 mcg/kg/hr

VAS for pain noted at the same times as group F

The primary outcome was the detection of significantly higher VAS for pain during dressing change on Postoperative

Day 2. Secondary outcome was requirement of rescue analgesic.

The data was analysed using Statistical Package for the social sciences (SPSS) version 21.0

Data for statistical analysis are presented as mean± standard deviation. A One Way ANOVA test was done to test for significance. In order to test the pair ways comparison Tukey HSD test is applied for VAS at dressing change. LEVENE S test for homogeneity of variance is 0.799.

RESULTS

Figure 1 shows the consort diagram for the flow of participants through each stage of the study. Sixty patients completed the study and were analysed for the study.

There were no statistically significant differences regarding the demographic data among the 3 groups (P >0.05) [Table 1].

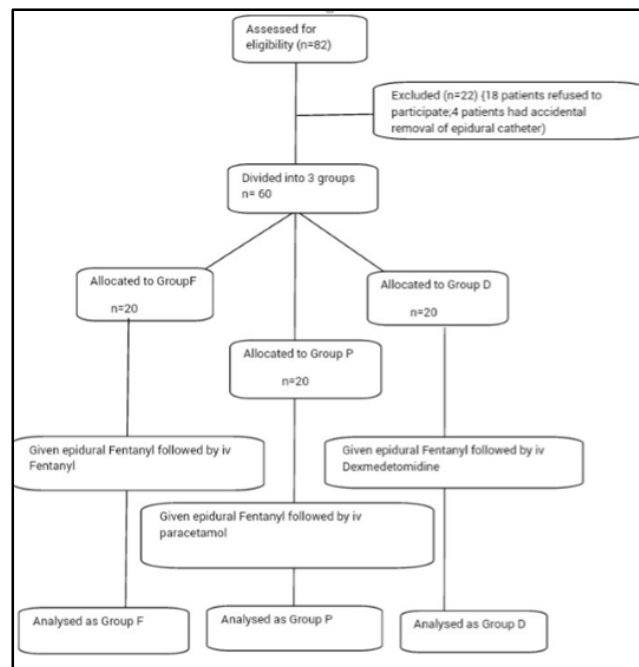


Figure 1. Consort Diagram for the Flow of Participants

Parameter	Group F	Group P	Group D	P value
Age (year)	42.72± 8.21	41.31 ± 6.88	43.56 ± 9.33	0.65*, 0.12**, 0.55***
Weight (kg)	66.09 ± 9.98	68.26 ± 10.24	69.54 ± 10.11	0.227*, 0.33**, 0.18**

Table 1: Comparison of the Demographic data of the 3 Groups

Group F: Fentanyl group; Group P: Paracetamol group; Group D: Dexmedetomidine group.

*Group F vs. Group P **Group P vs. Group D, ***Group D vs. Group F.

No statistically significant difference with respect to the Visual Analogue Score at 4, 12, 24 and 48 hrs (Figure 2).

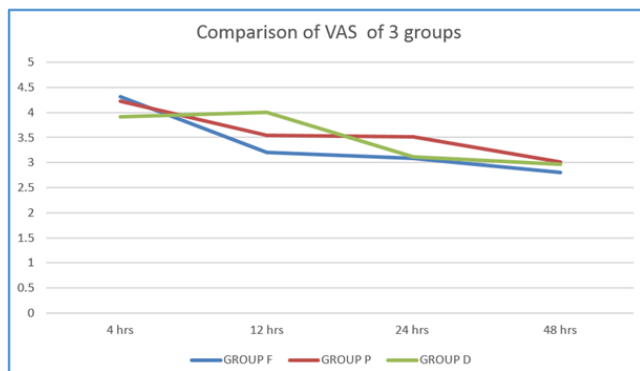


Figure 2. Comparison of VAS of the 3 Groups at 4H, 12H, 24H AND 48 HRS

VAS at dressing change: There is no significant difference between Group 2 and 3 but Group 1 significantly differs from both Group 2 and 3.

Group	N	VAS at Dressing	Change
1. Fentanyl only	20		4.20
2. Fentanyl followed by Paracetamol	20	3.05	
3. Fentanyl followed by dexmedetomidine	20	2.70	
Significance		0.29	1.00

Table 2. VAS at Dressing Change

DISCUSSION

Pain after abdominal hysterectomy is composed of the pain in incision site, pain from visceral structures, and dynamic pain due to conditions such as coughing and mobilization, and some of these components may be felt more than others at different times of post-operative period.⁵

The significantly higher pain scores during dressing change in the group receiving only fentanyl indicates the prevalence of opioid induced hyperalgesia following epidural fentanyl for two days.

Only a few clinical studies have examined OIH and fentanyl in opioid-naïve subjects undergoing a surgical procedure. Chia et al. examined 60 female American Society of Anesthesiologists I to II patients undergoing total abdominal hysterectomy, randomized to receive either 1 µg/kg or 15 µg·kg⁻¹·h⁻¹ fentanyl as a slow 20-min continuous infusion before the induction of anaesthesia. Although the visual analog scale was significantly higher in the high-dose group at 4 and 8 h after fentanyl administration, there was no statistically significant difference thereafter. Another study by Cooper et al. examined the effect of intrathecal fentanyl (25 µg vs. saline) for Caesarean section in 60 parturients.⁶ Although postoperative morphine requirements were higher at 6 h in the fentanyl group, pain scores did not differ statistically. A follow-up study with a similar design showed higher pain at rest-but not when coughing-for intrathecal fentanyl. Similarly, Carvalho et al. examined four different doses of intrathecal fentanyl in patients undergoing Caesarean

section and found dose-dependent differences in postoperative pain measured in the first 24 h, with higher doses of fentanyl associated with more pain.⁷

Opium and its derivatives have been used for centuries. Friedrich Serturmer discovered the major active ingredient of opium, which he named morphine and opioid pharmacology was born. Morphine and other opioid drugs act on an endogenous opioidergic system which is not only involved in setting pain (nociceptive) threshold and controlling nociceptive processing but also participates in modulation of gastrointestinal (GI) function, endocrine and autonomic function, and a possible role in cognition.⁸

Epidural opioid analgesia has become an important therapeutic technique in the management of acute pain and has been demonstrated to be superior or equal to other parenteral opioid techniques (intramuscular, intravenous, PCA) with less associated sedation and significantly smaller doses of drugs. Beneficial therapeutic effects of epidural opioids as a result of improved analgesia include improvement in pulmonary function, modification of the endocrine-metabolic stress response, and improvement in time to ambulation, decreased morbidity, and shorter hospital stay. The epidural administration of opioids is associated with potential side effects and complications, the most serious potential side effect being that of respiratory depression. This, as well as most of the other potential medication-related side effects associated with epidural opioid analgesia, is for the most part also associated with opioid analgesia provided by other routes of administration. These potential problems either occur rarely, or are controllable or preventable with appropriate patient selection and management. The potential benefits to the critical care patient as a result of the superior analgesia and reduced systemic effects associated with epidural opioid analgesia represent distinct medical and economic advantages, compared to conventional analgesic techniques.

FENTANYL was one of a series of opioids synthesized by Janssen Pharmaceutica in the 1950s and 1960s in an effort to produce opioid analgesics with enhanced analgesic activity and potency and fewer adverse effects compared with morphine or meperidine.^{9,10}

Fentanyl's popularity as an intraoperative agent relates directly to the cardiovascular stability it provides, even in critically ill patients.^{11,12} Fentanyl, N-(1-phenethyl-4-piperidyl) propionanilide, is structurally related to meperidine. Commercially, fentanyl is formulated as a citrate, available in a water-soluble, white crystalline powder that requires no preservatives. It has a molecular weight of 528.29 and a melting point of 148.5 to 150 [degree sign]C. Each millilitre of aqueous solution contains a base of 0.05 mg fentanyl (0.0785 mg of the citrate). Fentanyl is 100 to 300 times more potent than morphine per dose, depending on the animal species.^{13,14} This greater dose potency permits a low therapeutic blood concentration of approximately 0.6 to 3 ng/ml for analgesia

Fentanyl has both high lipid solubility and a pattern of rapid and extensive redistribution, making it an ideal agent for multiple routes of administration other than the traditional parenteral routes. Consequently, it has been administered via intramuscular, intravenous (bolus injection, infusion, patient-controlled analgesia [PCA]), neuraxial

(epidural, intrathecal), transdermal, transmucosal (oral or intranasal), and inhalational routes.

Epidural and intrathecal administration of fentanyl are long-established routes for intraoperative anaesthesia and postoperative analgesia. The pharmacokinetics of epidural delivery have been well-studied, but relatively little is known about the systemic kinetics of intrathecal fentanyl.

Pharmacokinetics

The main Routes of Distribution after Administration of Fentanyl into the Epidural Space Include-

1. Movement across the meninges into the cerebrospinal fluid (CSF);
2. Movement from the CSF into the opioid receptor or other nonspecific binding site in the spinal cord;
3. Rostral migration via the CSF to supraspinal sites;
4. Vascular absorption in the epidural or spinal vascular system; and
5. Uptake into epidural fat.

Factors that affect dural penetration include lipid solubility, molecular weight, molecular shape, and the degree of molecule ionization.^{15,16,17}

To cross the arachnoid mater, a drug molecule must diffuse through the hydrophilic domain (e.g., extracellular and intracellular fluid) and hydrophobic domain (e.g., cell membrane lipids). Lipophilic drugs readily dissolve in the lipophilic component of the arachnoid mater and thus cross the region easily. The hydrophilic zone is more difficult for these drugs to penetrate, creating the rate-limiting factor for diffusion via the arachnoid membrane. As a result, membrane permeability is highest in the opioids having intermediate lipid solubility (e.g., fentanyl). With continuous epidural infusion of fentanyl, clearance from the blood determines the blood concentration at steady state. Continuous infusion of doses resulting in good analgesia produces significant plasma fentanyl concentration (1 or 2 ng/ml) after several hours of administration. Studies comparing therapeutic doses of epidural and intravenous fentanyl for postoperative pain relief show similar plasma fentanyl concentration values at equal and equianalgesic doses

More than 40 published clinical trials document epidural fentanyl administration and effect. Most suggest that epidural fentanyl is less likely than morphine to produce clinically significant ventilatory depression. However, respiratory arrest has been reported. Fentanyl is reported to be associated with fewer minor adverse effects (nausea, vomiting, pruritus, sedation, urinary retention). The modes of epidural administration are the same as those used intravenously, i.e., bolus dose alone, bolus dose combined with continuous infusion, continuous infusion alone, PCEA, and PCEA with a continuous fixed or variable background infusion.

Hyperalgesia by definition is the enhanced response to pain from a stimulus that usually causes pain.¹⁸ In OIH, it is speculated that patients who originally take opioids for treating pain end up becoming more sensitive to certain painful stimuli.¹⁹ In other words, in addition to their analgesic effects, opioids can also result in paradoxical sensitization to painful stimuli. This type of pain experienced

in patients with OIH might be the same type of pain they take the opioids for or a different type of pain. That is opioids may cause paradoxical sensitization to painful stimuli.

Sensitization of Pronociceptive Pathways

Proposed Mechanisms of development of OIH

1. Central Glutaminergic System

It has been found in earlier studies that decreased reuptake of nociceptive neurotransmitters such as substance P and glutamate from the afferent fibres in the spinal cord and the increased responsiveness of the spinal neurons to such transmitters after chronic opioid intake have been implicated in the development of OIH.²⁰

2. Spinal Dynorphins

Spinal dynorphin, an endogenous opioid levels were shown to increase with continuous infusion of opioids like morphine.²¹ Increased levels of spinal dynorphin results in a release of spinal excitatory neuropeptides after a painful stimulus which in turn induces OIH.

3. Descending Facilitation

Rostral ventromedial medulla (RVM) is a part of the descending pathway, which modulates the transmission, and processing of painful stimuli at the level of the dorsal horn of the spinal cord. RVM has three different types of neurons; On-cells, Off-cells, and Neutral-cells, which respectively promote, inhibit, or have no effect on nociception processing in the dorsal horn of spinal cord.²² A study on rat animal models showed that chronic morphine exposure increases the number of the On-cells and promotes pain sensation via enhanced sensitization of the On-cells to painful stimuli

4. Decreased Reuptake and Enhanced Nociceptive Response

Decreased reuptake of nociceptive neurotransmitters such as substance P and glutamate from the afferent fibres in the spinal cord and the increased responsiveness of the spinal neurons to such transmitters after chronic opioid intake may have a role in the development of OIH

5. Genetic Mechanisms

When to Suspect OIH?

- When opioid treatment's effect seems to wane in the absence of disease progression, or
- Unexplained pain reports or diffuse allodynia unassociated with the original pain, or
- Increased levels of pain with increasing dosages.

Treatment

1. Increase the dose of opioid and evaluate for increased efficacy (tolerance)
2. Reduce or eliminate the opioid.
3. NMDA receptor antagonists.
4. Combination therapy with COX-2 inhibitors.
5. Alpha 2 receptor agonists.

Combined use of opioids with paracetamol and Nonsteroidal Anti-inflammatory Drugs is a known method in post-operative analgesia after total abdominal hysterectomy surgery.

Analgesic effect of intravenous paracetamol emerges after 5-10 min of application and reaches to maximum levels in 1 hr.²³

In literature, various studies performed in different surgical groups notified that intravenous paracetamol usage provided lower pain scores in the post-operative period.²⁴

Dexmedetomidine has become of the frequently used drugs in anaesthetic armamentarium, along with routine anaesthetic drugs, due to its haemodynamic, sedative, anxiolytic, analgesic, neuroprotective and anaesthetic sparing effects. Other claimed advantages include minimal respiratory depression with cardioprotection, neuroprotection and renoprotection, thus making it useful at various situations including offsite procedures.²⁵ α -1 to α -2 ratio of 1:1600 makes it a highly selective α -2 agonist compared to clonidine, thus reducing the unwanted side effects involving α -1 receptors.

The highly selective effect of dexmedetomidine promotes its use for intensive care unit (ICU) sedation. Reduced ICU stay, decreased duration of ventilation, haemodynamic stability and reduced agitation are claimed advantages.

There was no significant difference in pain scores in the groups receiving intravenous paracetamol and dexmedetomidine in the study.

CONCLUSION

Pain sensed by patients during dressing change was significantly more in patients receiving opioids alone as opposed to combination of opioids with paracetamol or dexmedetomidine. There was no statistical difference in pain sensed in patients receiving IV Paracetamol or IV Dexmedetomidine

REFERENCES

- [1] White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. *Anesth Analg* 2005;101(5 Suppl):S5-22.
- [2] Perniola A, Gupta A, Crafoord K, et al. Intraabdominal local anaesthetics for postoperative pain relief following abdominal hysterectomy: a randomized, double-blind, dose-finding study. *Eur J Anaesthesiol* 2009;26(5):421-429.
- [3] Lomessy A, Magnin C, Viale JP, et al. Clinical advantages of fentanyl given epidurally for postoperative analgesia. *Anesthesiology* 1984;61:466-469.
- [4] Benzon HT, Wong HY, Belavic AM, et al. A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. *Anesth Analg* 1993;76(2):316-322.
- [5] Zohar E, Fredman B, Phillipov A, et al. The analgesic efficacy of patient-controlled bupivacaine wound instillation after total abdominal hysterectomy with bilateral salpingo-oophorectomy. *Anesth Analg* 2001;93(2):482-487.
- [6] Cooper DW, Lindsay SL, Ryall DM, et al. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? *Br J Anaesth* 1997;78(3):311-313.
- [7] Chia YY, Liu K, Wang JJ, et al. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. *Can J Anaesth* 1999;46(9):872-877.
- [8] McDonald J, Lambert DG. Opioid receptors. *Continuing Education in Anaesthesia Critical Care & Pain* 2015;15(5):219-224.
- [9] Andrews CJH, Prys-Roberts C. Fentanyl-a review. *Clin Anaesthesiol* 1983;1:97-122.
- [10] Stanley TH. The history and development of the fentanyl series. *J Pain Symptom Manage* 1992;7(3 Suppl):S3-7.
- [11] Lunn JK, Stanley TH, Webster LR, et al. High dose fentanyl anesthesia for coronary artery surgery: Plasma fentanyl concentration and influence of nitrous oxide on cardiovascular responses. *Anesth Analg* 1979;58(5):390-395.
- [12] Stanley TH, Berman L, Green O, et al. Plasma catecholamine and cortisol response to fentanyl-oxygen anesthesia for coronary artery operations. *Anesthesiology* 1980;53:250-253.
- [13] Cookson RF, Towse GDW. The search for new analgesics. *Clin Res Rev* 1981;1:219-230.
- [14] Beckett AH, Casey AF. Synthetic analgesics: stereochemical considerations. *J Pharm Pharmacol* 1954;6(12):986-1001.
- [15] Moore RA, Bullingham RSJ, McQuay HJ, et al. Dural permeability to narcotics: in vitro determination and application to extradural administration. *Br J Anaesth* 1982;54(10):1117-1128.
- [16] Bernards CM, Hill HF. Physical and chemical properties of drug molecules governing their diffusion through the spinal meninges. *Anesthesiology* 1992;77(4):750-756.
- [17] Sandler AN. Clinical pharmacology and practical applications of spinal opioids. In: Bowdle TA, Horita A, Kharasch ED, eds. *The pharmacological basis of anesthesiology: basic science and practical applications*. New York: Churchill Livingstone 1994:149-178.
- [18] Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *Lancet Neurol* 2014;13(9):924-935.
- [19] Youssef F, Pater A, Shehata M. Opioid-induced hyperalgesia. *J Pain Relief* 2015;4(3):183.
- [20] Li X, Clark JD. Hyperalgesia during opioid abstinence: mediation by glutamate and substance p. *Anesth Analg* 2002;95(4):979-984.
- [21] Vanderah TW, Gardell LR, Burgess SE, et al. Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance. *J Neurosci* 2000;20(18):7074-7079.
- [22] Morgan MM, Heinricher MM, Fields HL. Circuitry linking opioid-sensitive nociceptive modulatory systems in periaqueductal gray and spinal cord with rostral ventromedial medulla. *Neuroscience* 1992;47(4):863-871.

- [23] Ferrante FM. Opioids. In: Ferrante FM, VadeBoncour TR, eds. Postoperative pain management. New York: Churchill-Livingstone Inc 1993:367-390.
- [24] Arici S, Gurbet A, Türker G, et al. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri* 2009;21(2):54-61.
- [25] Panzer O, Moitra V, Sladen RN. Pharmacology of sedative-analgesic agents: dexmedetomidine, remifentanyl, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. *Crit Care Clin* 2009;25(3):451-469.