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The Effect of Epidural Fentanyl-Bupivacaine Combined With Ultra Low Dose of Naloxone in Post-operative Pelvic Surgery

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Abstract:

Background: Epidural administration of Fentanyl is associated with multiple adverse effects, including respiratory depression, itching, and nausea. Adding ultra-low dose Naloxone can prevent the opioid-induced side effects, while preserving the analgesia.

Objective: The aim of the study is to outline the effects of epidural Fentanyl-Bupivacaine combined with ultra-low dose of Naloxone in post-operative pelvic surgery.

Patient and methods: Sixty patients, subjective to pelvic surgery, were randomly allocated to receive either Bupivacaine-Fentanyl or Bupivacaine-Fentanyl combined with ultra-low dose Naloxone (30 patients for each group).

Intervention:. This was a randomized double-blind, uniform crossover, controlled clinical trial. The patients were treated with mixture of Bupivacaine-Fentanyl or mixture of Bupivacaine-Fentanyl combined with ultra-low dose Naloxone.

Main outcome measure: The primary goals were to evaluate pain after epidural injection of Bupivacaine-Fentanyl or Bupivacaine-Fentanyl combined with ultra-low dose Naloxone.

Secondary end-points were the incidence and the side effects (pruritus, PONV, hypoventilation) after epidural injection of Bupivacaine-Fentanyl or Bupivacaine-Fentanyl combined with ultra-low dose Naloxone.

Results: Pain was significantly lower in the Naloxone group at 8, 16, and 32 hours postoperatively. Nine patients in control group had grade 5 pruritis compared to no patients in Naloxone group. Subsequently, mild pruritis was higher in Naloxone group compared to control group, as grade 1 has 66 patients in Naloxone group and 28 patients in control group. Adding ultra-low dose of Naloxone decreased the incidence of postoperative nausea and vomiting, but the difference was only significant at 16 hours postoperatively. There was a statistically significant difference between the groups, regarding the alertness score at 2 and 4 hours postoperatively. Hypoventilation was lower in the Naloxone group but the difference was not statistically significant.

Conclusion: Concomitant epidural administration of an ultra-low dose of Naloxone should be considered to reduce the opioid-induced side effects. Naloxone preseved analgesia and reduced pruritus, PONV, and respiratory depression.

Key words: *Epidural Fentanyl-Bupivacaine, ultra-low dose Naloxone, post-operative pelvic surgery.*

Introduction:

Epidural analgesia acts as a neuraxial regional block and is used extensively in thoracic, abdominal, and pelvic surgeries for optimal postoperative pain control. Indeed, postoperative pain control has become an important part of acute pain management because of its effects on postoperative patient recovery. Evidence from previous studies indicates that effective postoperative pain control can reduce patient morbidity and affect the patient outcome

Compared to IV Patient Controlled Analgesia (PCA) [1.], Continuous Epidural Analgesia (CEA) has been reported to have a better pain control in the first 72 hours after abdominal surgery[2]. Supportingly, a subsequent meta-analysis of randomized controlled trials comparing the two modes of opioid delivery in colorectal surgery showed that CEA significantly reduced the postoperative pain and ileus, but was associated with pruritus, hypotension, and urinary retention[3]. Indeed, epidural opioid administration has several adverse effects, including respiratory depression, itching, and nausea. Both analgesia and the side effects of opioids are dose-dependent; therefore, reduction of opioid consumption by the use of multimodal analgesia can attenuate side effects and improve analgesia.This has led to attempts to combine epidural opioid with

epidural administration of drugs such as Butorphanol And Droperidol in the hope of minimizing side effects.

The exact mechanism of this analgesic effect of ultra-low doses of Naloxone is not fully understood.Some studies have illustrated that in contrast with usual standard doses, ultra-low doses of Naloxone selectively block the excitatory effect of opioids. Indeed, the desirable antinociceptive effects of the ultra-low dose Naloxone may be attributable to one of the following mechanisms: (1) low-dose Naloxone may enhance the release of endogenous opioid peptides by blocking presynaptic autoinhibition of Enkephalin release 4 and (2) low-dose Naloxone directly and competitively antagonizes the Gs protein-coupled excitatory opioid receptors that are responsible for the hyperalgesia occasionally reported with opioid administration without attenuating inhibitory Gi/Go-coupled opioid receptors mediating analgesia.

Interestingly, some in-vitro evidence, alongside with animal and human clinical studies, demonstrated that the ultra-low dose of intravenous (IV) opioid antagonists, along with opioids, could increase analgesia. In addition, the ultra-low dose of Naloxone resulted in reduction of opioid-induced side effects, such as vomiting, nausea, pruritus, and respiratory depression[4]. The administration of an ultra-low dose Naloxone, combined with opioid, decreased opioids consumption; yet in some studies, there were no significant differences in the incidence of the opioids' adverse effects. Furthermore, in-vitro studies indicated that the intrathecal Naloxone effectively inhibited the visceromotor response to Morphine[5], whilst the analgesic effects of epidural Morphine can be inhibited by epidural Naloxone[6].

Overall, the effect of epidural Naloxone on analgesic effect of Fentanyl and the incidence of side effects have not yet been established. We hypothesized that there was a relationship between the epidural Naloxone doses that would minimize side effects in patients receiving epidural pain control with Fentanyl and Bupivacaine without reversing analgesia.

Aim of the Study:

The aim of the study is to outline the effects of epidural Fentanyl-Bupivacaine combined with ultra-low dose of Naloxone in post-operative pelvic surgery.

Patients and Methods:

This study was conducted in Al-AZhar University Hospitals, Department of Anaethesia and Intensive Care, Faculty of Medicine, boys (Cairo). The study was approved by the Ethical Committee of the hospitals.

Patients:

After approval of medical ethics committee and a written informed consent was obtained from every patient after explanation of the objective and the details of the study to them, I included 60 patients, subjective to pelvic surgery, and receiving either Fentanyl-Bupivacaine alone or combined with ultra-low dose of Naloxone. Exclusion criteria will include:

1. patient refusal.
2. Preoperative coagulation abnormality.
3. Severe systemic infection.
4. History of allergy to bupivacaine, fentanyl or naloxone.
5. Patients' inability to understand the use of patient-controlled analgesia.

This study will include (60) patients divided into 2 groups:

1**. Group A (control group):** (30) cases will be given an analgesic solution of Bupivacaine (0.05%) and Fentanyl (4µg/ml).

2. **Group B (study group):** (30) cases will be given an analgesic solution of Bupivacaine (0.05%), Fentanyl (4µg /ml) and ultra-low dose Naloxone 0.04 mg.

Methods:

After proper sterilization, the epidural catheters were placed before operation at a vertebral level corresponding to the dermatomal level of the surgical incision. A 18-gaugc Touhy needle and 20-gauge epidural catheter were used. Loss-of-resistance technique was considered to identify the epidural space, and the epidural catheter was placed 3-7 cm into the epidural space. The catheter was affixed using skin adhesive, followed by a sterile dressing. Before admission, all patients fasted for 8 hours, according to the fasting guidelines. After preoperative assessment by clinical examination and laboratory investigations and on arrival to the operating room, a peripheral intravenous cannula (20-G) was inserted in the nondominant hand; pre-medications were given in the form of Ondansetron 4 mg, Midazolam 0.04mg/kg, and Fentanyl 2 µg/kg.

Anesthetic technique:

After preoxygenation for 3min, general anesthesia was induced with Propofol 2 mg/kg, tracheal intubation was performed after 3 min following administration of a nondepolarizing neuromuscular blocking drug Atracurium 0.5 mg/kg, and general anesthesia was maintained with 1.2% Isoflurane in oxygen and Atracurium 0.1 mg/kg/h infusion. Volume-controlled ventilation was used to maintain O2 saturation more than 98% and end tidal CO2 35–40 mmHg. Overall, 50 µg of Fentanyl was given when heart rate or blood pressure increased by 20% from the baseline reading, and Ephedrine 10 mg if blood

pressure decreased by 20% from the baseline. Continuous monitoring was done during the procedures using GE Datex-Ohmeda (GE Healthcare, Chicago, Illinois), which involved 5-lead ECG, noninvasive blood pressure, pulse oximetry, and end-tidal CO2.

1. All patients will be transferred from the post-anesthesia care unit to the surgical ward unless surgical practice required intensive care observation.
2. An analgesic solution of Bupivacaine (0.05%) and Fentanyl (4 µg /ml) was used for control group.
3. An analgesic solution of Bupivacaine (0.05%), Fentanyl (4 µg /ml) and ultra-low dose of Naloxone (0.04 mg).

Initial PCEA settings will be a background infusion of 4 ml/h with a PCEA bolus of 2 ml and lockout interval of 10 min. Inadequate analgesia (verbal pain score at rest >5) will be treated with a 5-ml loading dose of the Bupivacaine plus Fentanyl solution followed by an increase in the background infusion of 2 ml/h. Adjuvant analgesics such as Ketorolac, and Paracetamol will be allowed at the discretion of the APS (Anathesia Professional Service).

Initial data collection will include patient's sex, age, BMI and type of surgical procedure.

The following prospective data will be collected by the APS during visits:

Measurment include:

1. **Pain assessment**:Visual analog scale (0.0 = no pain, 10.0 = worst pain imaginable. Pain assessment will be done every hour for 6 hours then every 6 hours for the next 24 hours. Ketorloc will be administered by IV injection if (VAS score >4 mm).
2. **Hypoventilation:**Sedation will be judged by the observer on a five-point scale, every hour for 6 hours then every 6 hours for the next 24 h.
   0 = alert.
   1 = mildly drowsy.
   2 = moderately drowsy, easily rousable.
   3 = very drowsy, rousable.
   4 = difficult to rouse.
   5 = unarousable .
3. **PONV:**Presence of nausea will be defined as patient request for antiemetic treatment.
4. **pruritus:** The presence of pruritus will be defined as patient requests for antipruritic treatment.

Statistical analysis of data:

Data will be collected by APS team. Data collection will be initially recorded on a standardized paper form and then transferred to a computer database (Excel 5.0; Microsoft Corporation, Redmond. WA). The effects of the treatment were evaluated at each point using the Kruskal-Wallis statistic. The

Mann-Whitney U test was used to determinewhether significant differences existed among groups and the specific inter-group differences were identified accordingly. The incidence of the non parameteric data like ASA and hypoventilation were compared using the chi-square test. Two-tailed $P < 0.05$ was considered to be significant.

Results :

Out of the 97 patients recruited to participate to the study, 37 were excluded before randomization because they did not meet the inclusion criteria. Of the remaining 60 eligible patients, all agreed to participate. No statistically significant difference was reported, regarding age, gender, weight, height and ASA classification. Comparisons of the baseline variables of the randomized groups are represented in (Table1) .

Table 1: Patients demographic characteristics.

Demographic data	Naloxone group (n=30) F=25 and M= 5	Control group (n=30) F=24 and M= 6	P-value
Age (years)	35.7±9.3	38.3±7.8	0.372
Weight (kg)	53.5±3.3	55.9±3.7	0.141
Height (cm)	155.7±3.4	153.2±2.6	0.472
ASA			
I	24 (80.0%)	27 (90.0%)	
II	6 (20.0%)	3 (10.0%)	0.295

Pain assessment :

We used the VAS pain score to subjectively assess pain grade throughout the procedure. Patients in the Naloxone group reported lower grades of pain at all the time points. The difference was statistically significant at 8, 16 and 32 hours postoperatively (Fig. 1).

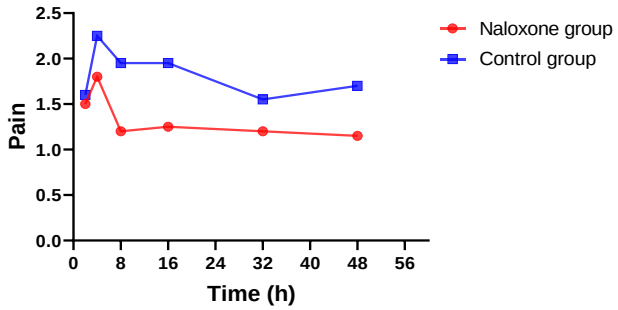

Fig1:Mean pain score regarding postoperative timeline.

Side effects :

Regarding pruritus, there was significant higher numbers of patients with severe pruritis in the control group, compared to the Naloxone group. Nine patients in control group had grade 5 pruritis compared to no patients in Naloxone group. Subsequently, mild pruritis was higher in Naloxone group compared to control group, as grade 1 has 66 patients in Naloxone group and 28 patients in control group (Fig.2). Therefore, the severity of pruritis decreased after using Naloxone. In addition, the mean pruritus score was lower in the Naloxone group, compared to the control group with significant difference at 8, 16, and 32 hours postoperatively (Fig. 3).

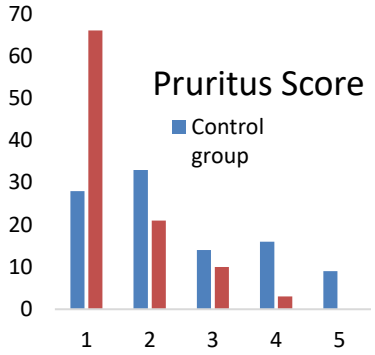

Fig.2: Pruritis score distribution among study groups.

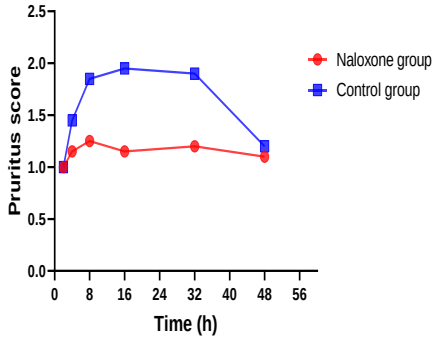

Fig.3: Mean pruritis score regarding postoperative timeline.

Postoperative nausea and vomiting (PONV) mean values were lower in the Naloxone group, compared to the control group at all time points, whilst the difference was only significant at 16 hour (Fig. 4). Furthermore, there was a statistically significant difference between the groups, regarding the alertness score at 2 and 4 hours postoperatively (Fig. 5) .

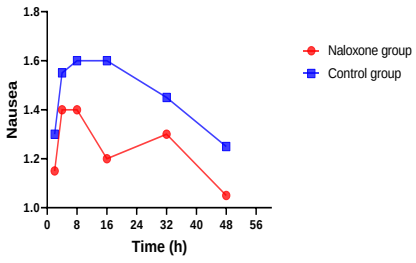

Fig.4: Mean nausea score regarding postoperative. Timeline

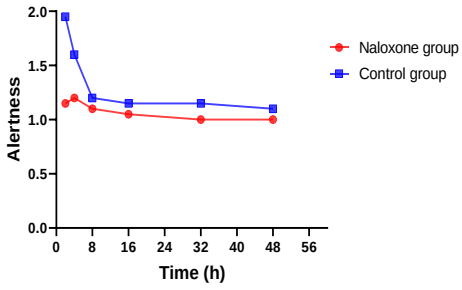

Fig.5: Mean alertness score regarding postoperative timeline.

Hypoventilation was reported in 5 cases in the control group, compared to only one case in the Naloxone group 4 hours following the surgery, which was not statistically significant (Table 2) .

Table 2: Trends of hypoventilation throughout the procedure

Hypoventilation	Naloxone group (n=30) F=25 and M= 5	Naloxone group (n=30) F=26 and M= 4	p-value
Preoperative	0	0	0.136
After 2 hr	1 (3.3%)	4 (13.3%)	0.21
After 4 hr	0	1 (3.3%)	0.158
After 8 hr	0	0	0.062
After 16 hr	0	0	0.052
After 32 hr	0	0	0.079
After 48 hr	0	0	0.217

Discussion :

The results of this study indicated that the concomitant epidural infusion of Fentanyl and Naloxone for postoperative analgesia not only reduces the incidence and severity of PONV but also enhances the analgesic effect of Fentanyl. At present, opioids like Morphine and Fentanyl are the most analgesic drugs utilized in clinic. Fentanyl features a short time of taking effect, a brief maintenance time, relatively few side effects, and a stronger analgesic effect. Its analgesic effect is 80 to 112 times of that of Morphine. This is the rationale for the utilization of Fentanyl in postoperative analgesia.

Epidural analgesia is taken into account by many because the gold standard analgesic technique for operation. It has the potential to supply patients with complete analgesia for as long because the epidural is sustained. This is usually achieved with a mixture of epidural local anesthetic and an opioid. Importantly, the epidural techniques are particularly effective at providing dynamic analgesia, allowing the patient to mobilize and resume normal activities unlimited by pain.

Parenteral opioids, even with patient-controlled delivery systems, can't predictably provide an equivalent quality of analgesia.

My study suggested that the overall VAS pain scores were lower in the Naloxone group, and the difference was statistically significant at 8, 16 and 32 hours after the surgery. Supportingly, a study conducted by AEl-Garhy, A. M., & Nouh, E. M.[7] investigated the effect of adding ultra-low-dose Naloxone to the local anesthetic on postoperative pain relief in patients undergoing laparoscopic cholecystectomy, and found that the ultra-low-dose Naloxone usage in TAP block helps in reducing postoperative pain scores and postoperative opioid consumption. Recently, some animal and human evidence has indicated that ultra-low doses of Naloxone have some analgesic properties. This result was in agreement with Cepeda MS and Alvarez H[8], who found that the combination of ultra-low-dose Naloxone and Morphine in PCA does not affect analgesia or opioid requirements, but it decreases the incidence of nausea and pruritus. In addition, ultra-low-dose Naloxone not only potentiates the analgesic efficacy of the local anesthetic, but also prolongs the duration of analgesia. This was consistent with the study conducted by El-Garhy, A. M., & Halim, N. E.[9], who compared ultra-low-dose Naloxone versus Dexmedetomidine with local anesthetic in peribulbar block in cataract surgery, and showed that ultra-low-dose Naloxone had longer duration of analgesia. Indeed, Naloxone had a biphasic dose-dependent effect on pain, low doses of Naloxone enhance opioids' analgesic effects, while high doses reverse the analgesia and produce hyperalgesia[10].

The exact mechanism of this analgesic effect of ultra-low doses of Naloxone is not fully understood. However, some suggestions have been proposed. Some studies have illustrated that in contrast with usual standard doses, ultra-low doses of Naloxone selectively block the excitatory effect of opioids[11]. Indeed, the desirable antinociceptive effects of the ultra-low dose Naloxone may be attributable to one of the following mechanisms: (1) low-dose Naloxone may enhance the release of endogenous opioid peptides by blocking presynaptic autoinhibition of Enkephalin release 4 and (2) low-dose Naloxone directly and competitively antagonizes the Gs protein-coupled excitatory opioid receptors that are responsible for the hyperalgesia occasionally reported with opioid administration without attenuating inhibitory Gi/Go-coupled opioid receptors mediating analgesia[12]. Furthermore, it is likely that an ultra-low dose of Naloxone augments the antinociceptive effect of opioids by intensifying the reuptake of the excitatory amino acids (EAAs) from the synaptic cleft[13].

Regarding PONV, my study highlighted that the moderate to severe PONV was significantly lower in the Naloxone group, compared to the control group. Severe PONV was significantly higher in the control group (24.4% and 11.1%),

with no detected cases in the Naloxone group at 16 and 32 hours respectively. Supportingly, several studies showed that the administration of ultra-low dose Naloxone may influence the incidence of opioid side effects such as nausea, vomiting, and pruritus. This result was in agreement with the results of (Movafegh et al., 2012), who proved that ultra-low -dose of naloxone infusion reduced morphine consumption as well as the incidence and severity of opioid induced nausea and vomiting after hysterectomy. On the other hand, some studies failed to show any reduction of post-operative opioid side effects by ultra-low-dose Naloxone. One study indicated that ultra-low-dose Naloxone given prior to the injection of spinal Bupivacaine did not have an effect on the incidence of PONV[14]. Sadeghi et al, studied the effect of an intravenous bolus of ultra-low-dose Naloxone on intraoperative sedation, post operative pain intensity and Morphine consumption in cesarean delivery patients under spinal anesthesia, and concluded that there were no significant differences in the incidence of PONV and pruritus in groups. Importantly, PONV is a major concern in opioid analgesia because patients rated PONV as the most undesirable side-effect and indicated that the avoidance of PONV was of a higher priority than avoidance of postoperative pain[15]. In addition, Fentanyl can excite the medulla oblongata center, and increase the sensitivity of the vomiting center by stimulating the vestibular nerve system, causing nausea, vomiting, and other discomforts. Bamigbude and Langford considered that the disorder of gastric and duodenal motility caused by opioid receptor agonists was one of the main causes of nausea and vomiting[16]. Moreover, the foremost commonly identified risk factors for PONV include female gender, non-smoking status, history of PONV or kinetosis, extended duration of anaesthesia, postoperative opioid use, and age[17]. Roberts and colleagues reported that both postoperative opioid use and female gender significantly influenced PONV, whereas opioid use, in particular, had a dose-dependent relationship with PONV.

We evaluated the distribution of pruritis score throughout the procedure, and found that adding an ultra-low dose Naloxone to epidural Fentanyl significantly reduced the pruritis score at 8, 16, and 32 hours after surgery. Indeed, The exact mechanism of pruritus is not clear; medullary dorsal horn activation may be related to pruritus. Supportingly, in one human study, epidural Naloxone reduced neuraxial Fentanyl-induced pruritus during labor analgesia[18]. There have been previous reports of the antipruritic effect of Naloxone, but the methods used and their results are variable. In most studies, Naloxone was administrated intravenously. Naloxone given by intravenous bolus injection, or by continuous intravenous infusion, has been found to be effective in reducing pruritus caused by epidural or intravenous Morphine. However, Cepeda M S [19] and Sartain J B[20] found intravenous injections of Naloxone to be without beneficial effect.

Regarding respiratory depression, 5 cases in the control group showed hypoventilation, compared to only one case in the Naloxone group 4 hours following the surgery, which was not statistically significant. This result was consistent with the results of Choi J H[21] who found no statistically significant difference between the opioid and Naloxone groups. Supportingly, Nekoui A and his colleagues[22] found that there was no statistically significant difference between the opioid and Naloxone groups on respiratory depression and oxygen saturation. They concluded that Naloxone did not have any effects on respiratory function. Nevertheless, an epidural opioid dose-related respiratory depression was well documented[23]. Consequently, higher doses of Naloxone may be required to reverse the opioid-induced respiratory depression.

Our study had some limitations. First, the blood concentration of Naloxone was not measured. Second, this study was not powered for pruritus evaluation. Third, as our patients had bladder catheters, the assessment of Fentanyl-induced urinary retention and the possible effect of ultra-low-dose Naloxone on the incidence of this side effect were not feasible. Fourth, the dose-response relationship of Naloxone when administered into the epidural space was not assessed.

In conclusion, the epidural administration of ultra-low dose Naloxone was effective in reducing pruritus, PONV induced by epidural Fentanyl, and additionally enhances its analgesic effect. Further studies are needed to establish a better understanding of the mechanisms of this phenomenon. Consequently, concomitant infusion of an ultra-low dose of Naloxone should be considered to reduce PONV, especially in patients at greater risk for them .

Conclusion:

Concomitant epidural administration of an ultra-low dose of Naloxone should be considered to reduce the opioid-induced side effects. Naloxone preseved analgesia and reduced pruritus, PONV, and respiratory depression.

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