Epidural naloxone to prevent Buprenorphine induced PONV

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Citation

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Abstract

Epidural infusion of local analgesic and opioid are commonly used for postoperative pain relief. This combination gives excellent anlgesia but nausea and vomiting remains a major concern. Low dose epidural naloxone prevents PONV induced by spinal opioids like morphine, fentanyl and sufentanil. However, it is not known that epidural naloxone administration prevents PONV induced by epidural buprenorphine. We have reported three of our cases of major abdominal operation in which lowdose epidural infusion of naloxone releived the symptom of buprenorphine induced severe PONV and improved the quality of analgesia.

INTRODUCTION

Background: Buprenorphine is a popular choice for epidural analgesia because it gives longer duration of pain relief with comparatively less side effects [1,2]. We routinely use buprenorphine and bupivacaine mixtuer either bolus or continuous infusion by syringe pump for postoperative analgesia in major gynecological surgery. This mixture gives an excellent quality and duration of analgesia (6-10 hrs.) for each bolus, however large number of patients (30-40%) complain nausea and vomiting particularly on repeated bolus or on continuous infusion. Epidural naloxone has been used to prevent PONV induced by epidural opioids like morphine [3], and sufentanil[4]. We have investigated the effect of low dose epidural infusion of naloxone on buprenorphine induced PONV in hysterectomy patients.

Case-1: A 38 yr old ASA- I female wt 64 Kg, had hysterectomy operation under combined spinal epidural anaesthesia and received bupivacaine and buprenorphine mixture for postoperative pain relief. Needle through needle technique (CSE Cure, Portex Combined Spinal/Epidural mini pack 27G/18G) was used to give anaesthesia. Epidural needle placed with loss of resistance to air technique at L3/L4 space and Subarchnoid block was given with 0.5% heavy bupivacaine 4 ml by 27G whitacre pencil point needle than epidural catheter 18G was inserted 3-4 cm cephalad and flushed with 1 ml saline after negative aspiration for blood and CSF. No intra-operative top-up was required. In postoperative ward, patient started complaining of pain VAS score was 6-7/10, 3 ml of 1% xylocaine with adrenaline was given epiduraly as test dose and after ten minutes, five ml mixture of 0.125% bupivacaine + 150 µg buprenorphine was given. After 30 minutes (epidural was effective VAS=4) infusion of 0.125% bupivacaine + buprenorphine 5 µg/ ml was started with syringe pump at 4 ml/ hr. Injection Ondansetron 4 mg IV for vomiting, and Injection Diclophenac 75 mg IM or 5 ml bolus of infusion mixture for pain (VAS >3) was advised as rescue analgesic on demand basis (decided by observer anaesthetist). Two hourly Visual analog score was done for pain (scale 0-10) and for vomiting (scale 0-5) for 24 hrs, then 4 hrly for 48 hrs. If patient found sleeping Zero score was given for pain and PONV. However, if complained of pain or PONV occurred in between it was included in near by time record. After one hour of epidural injection patient started severe nausea and repeated vomiting (4 times in one hr, PONV score=5.), complain of uneasiness and malaise. Injection Ondansetron 4mg , was given and after 20 minutes when vomiting did not stop Injection Metoclopramide 10 mg + Dexamethasone 8 mg was given. After 2 hrs. of treatment vomiting stopped but severe nausea (PONV score=2) and uneasiness persisted. After eight hours of first epidural injection patient started complaining of pain(VAS=8-9/10). This time we gave 5 ml epidural mixture of 0.125% bupivacaine+ 25 µg buprenorphine+ 16.5 µg Naloxone (30 ml 0.25% bupivacaine+ 300 µg buprenorphine+ 200 µg naloxone+ 28 ml saline=60 ml solution) and infusion of same mixture was started at 4 ml/hr (effective dose of buprenorphine=

0.31µg/kg/hr, and naloxone 0.20µg/kg/hr). Patient was observed for next 36 hours and no episode of PONV occurred. Patient reported better pain relief and physical comfort this time. Pain score remain 0-2 during this infusion regimen.

Case-2: A 41 yr old, 62 kg female, with the history of fibroid uterus scheduled for hysterectomy. She had two previous operations and reported excessive PONV lasted for >36 hrs postoperatively even with entiemetic prophylaxis and treatment , in both the operations. Hysterectomy was done under combined spinal epidural technique (needle through needle, CSE Cure, Portex), and postoperative analgesia was provided as per protocol used in previous case. However, this time 60 ml 0.125% bupivacaine solution containing (Inj. Naloxone 200 µg + 300 µg buprenorphine) was started from beginning at the rate of 4 ml/hr (the dose of naloxone = 0.2µg/kg/hr, and buprenorphine = 0.31µg/kg/hr) . Visual analog score was done. Patient had nausea (PONV score= 1), just after taking biscuits and tea 6 hrs after operation, otherwise she never had nausea or vomiting in 48 hrs of observation period (PONV score remain=0). Pain relief was excellent as score was 0-2). She was highly satisfied with present pain relief and quality of comfort.

Case-3: A 37 yr. and 59 kg , ASA- II patient undergone Right ovarian cystectomy + abdominal hysterectomy under epidural analgesia. Epidural catheter(18G , Perifix 400 mini set, B/Braun)) was inserted through L3/L4 space directed up-wards 4 cm. Anaesthesia was provided by 16ml (1:1 mixture of 2% xylocaine with adrenaline and 0.5% bupivacaine) after 3ml test dose of 1% xylocaine with adrenaline. During skin closure when patient complained of discomfort, 4 ml of similar solution + 150 microgram buprenorphine was given through epidural catheter. Postoperative monitoring for PONV and pain was done as per protocol. After 2 hours of operation patient complained of sever nausea and uneasiness (PONV score=3). She received inj. Ondansetron 4 mg IV, Pain score was 5-7 on the scale of 10. She vomited once, nausea and discomfort (uneasiness & giddiness) was increasing (PONV score4). Infusion of naloxone 4 µg/ ml (200 µg in 50 ml normal saline) was started at 4 ml/ hr (0.27µg/kg/hr). After 30 minutes the intensity of nausea was decreased (PONV score= 1) and after 1 hr patient was comfortable and free from nausea(PONV score=0). Pain relief was also better (VAS 0/10). This infusion was continued for 6 hrs, than bupivacaine and buprenorphine were mixed in same syringe for postoperative pain relief to get concentration of 0.125% bupivacaine and dose of buprenorphine 0.3µg/kg/hr and naloxone 0.20 µg/kg/hr. Rest of the postoperative period was uneventful pain score remain 0-2/10 and patient was highly satisfied with pain relief.

DISCUSSION

Epidural buprenorphine is an effective analgesic but PONV is very common undesirable side effect [5]. Buprenorphine and other opioid drugs cause PONV by action on MOR (µ opioid receptor) present in the brain and gastro intestinal tract [6]., Buprenorphine is a semi-synthetic opioid with agonistic activity at the MOP-receptor and antagonistic properties at the KOP-receptor. Human studies show that buprenorphine behavior is typical of MOP-receptor agonists, with respect to its intended effect (potent and long-lasting analgesia) and side-effects (e.g. it causes sedation, nausea, delayed gastric emptying) but a partial agonist at MOP receptors involved in respiratory depression. Buprenorphine's behavior may be due to difference in the agonist/MOR/G-protein/-arrestin complex in pain and respiratory neurons.[7]

Naloxone is an opiate receptor antagonist has been used through intravenous and epidural route to counter opioid induced side effects like itching, nausea vomiting, decreased intestinal motility and respiratory depression. By titration of naloxone doses it is possible that, only side effects (PONV, itching, respiratory depression etc.) are controlled and opioid analgesia is retained [3,4,8].

The possible mechanism include, (a) low dose naloxone may enhance release of endogenous opioid peptides by blocking presyneptic autoinhibition of encephalin release[9] and, (b) low dose naloxone directly and comptetively antagonize the Gs protein-coupled excitatory opioid receptor that are responsible for the hyperalgesia occasionally reported with opioid administration without attenuating inhibitory Gi/Go-coupled opioid receptors mediating analgesia [10]. Whether similar mechanism also active with co-administration of naloxone and buprenorphine is not documented however, experimental studies have shown the efficacy of intrathecal naloxone to couneract effects of buprenorphine administered intrathecally [11]. We used infusion of naloxone after initial bolus instead of only bolus because it is better to infuse naloxone continuously as it has half life of 55 minutes and intermittent administration will result in fluctuation of concentration [12]. There was no previous guideline available for epidural dose of naloxone to prevent PONV with buprenorphine. We have used an average dose of 0.20-0.27 µg/ kg/hr, considering that, this will be low dose as similar

dose has been used to prevent sufentanil induced PONV [4]. Regarding safety of naloxone for spinal use, various experimental and clinical studies have shown that naloxone not only safe for spinal use rather it is neuroprotective [13].

So far clinically reduction in nausea, vomiting and analgesia enhancing effect with low dose naloxone have been noticed only with pure mu agonist like morphine, fentanyl and sufentanil. In present report, we have observed that similar effects were seen when naloxone interacted with partial mu agonist buprenorphine, as all three patients responded in similar and predicted manner. Symptoms of PONV were controlled and quality of analgesia improved.

Pharmacology of buprenorphine is very complex and still poorly understood. This case report highlights the possibilities that, epidural administration of naloxone may help in management of epidural buprenorphine induced PONV and may enhance analgesic effect of epiduraly administerd buprenorphine. However to prove this hypothesis, a large RCT along with receptor binding analysis studies are required.

CONCLUSION

We noticed improvement in pain score with relief of nausea and vomiting when low dose naloxone used epiduraly to control buprenorphine-induced nausea and vomiting. However, with only three cases observed, further detail study is required to reach any conclusion.

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