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Research Article

Is the combination of epidural clonidine–levobupivacaine has same analgesic efficacy and safety as the combination fentanyl–levobupivacaine after radical cystectomy?

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KEYWORDS

Epidural;
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Abstract *Objective:* This study was conducted to compare the efficacy and safety of addition of two drugs; clonidine versus fentanyl to epidural levobupivacaine to control postoperative pain after radical cystectomy surgery.

Patients and Methods: All urinary bladder cancer patients of both sex, ASA I and II, 40–70 years undergoing radical cystectomy surgery in National Cancer Institute (NCI) from November 2011 till May 2012 are the target group of which 50 patients accepted to share in the study, they are randomly classified by permuted block technique into two groups; group C (clonidine) who received 6 ml of levobupivacaine 0.25% + clonidine 75 μg epidural bolus dose followed by continuous epidural infusion of levobupivacaine 0.125% + clonidine 2 μg/ml at a total rate of 6–10 ml/h, and group F (fentanyl) who received 6 ml of levobupivacaine 0.25% + fentanyl 50 μg bolus dose followed by continuous epidural infusion of levobupivacaine 0.125% + fentanyl 2 μg/ml at a total rate of 6–10 ml/h. Paracetamol 1 g IV infusion was used as a rescue pain treatment. In both groups epidural activation is done after complete recovery from balanced general anesthesia. In both groups we measured vital signs (HR, MBP, RR), 0–10 visual analogue scale (VAS) and Sedation using the four-point Ramsay Sedation Scale are assessed for first 24 h postoperatively. In addition we recorded the total 24 h rescue paracetamol dose needed and side effects of both drugs were also observed.

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Results: We found that there is no statistical significant difference between both groups in the vital signs (HR, MBP, and RR), analgesic efficacy (VAS), and Sedation effects (Sedation Scale), and all data were within clinically accepted range. There was no statistically significant difference in total 24 h paracetamol rescue dose needed in both groups with the same range (1–3 g/24 h) and same median value (2 g/24 h). Recorded side effects were minimal and insignificant in both groups.
Conclusion: We concluded that both clonidine and fentanyl can be used as effective additive to epidural levobubivacaine for postoperative analgesia after radical cystectomy with no significant difference between them in vital signs, analgesic, sedative effects and safety profile on adding each of them in doses not exceeding 20 μg/h to epidural continuous levobupivacaine infusion.

1. Introduction

Control of postoperative pain is an important concern of anesthesiologists [1]. One of the good methods is multimodal pain therapy "balanced analgesia" based on the hypothesis that a combination of analgesics with different sites of action may improve overall pain relief [2]. Epidural administration of combined local anesthetics and opioids may provide improved pain relief but still carries the risk of side effects when doses approach levels necessary for total pain relief [3–7].

Levobupivacaine, the pure S-enantiomer of bupivacaine, is theoretically safer alternative than its racemic parent [8,9]. It has been claimed to be more potent than bupivacaine [10,11] or ropivacaine [12], in addition to cause less motor impairment [13–15], however little difference was found by evidence based medicine to support this [10].

Clonidine, an α2-adrenergic agonist, reduces but does not eliminate pain after surgery [16–18]. However, with high doses of clonidine, significant hemodynamic depression with hypotension was observed [16–18].

Several studies have been published describing the anesthetic-sparing effects and analgesic properties of epidural clonidine [19–21]. Several reports of epidural clonidine have focused on the optimal doses of clonidine to be used [22–24], rather than analyzing the potential advantages of using epidural clonidine versus opioids with respect to efficacy and incidence of side effects [21,25].

Epidural fentanyl has been used effectively as an alternative to morphine and has been shown to induce fewer complications when compared with epidural morphine [26,27].

The addition of clonidine to epidural local anesthetic as an adjuvant to prolong analgesia has been studied extensively since 1984, by the study of Tamsen and Gordh published in Lancet [28]. However few studies investigated the effect of adding clonidine to levobupivacaine.

The aim of this study was to compare both analgesic efficacy and side effect profile of epidural clonidine versus fentanyl when each of them is added to epidural levobubivacaine.

2. Patients and methods

Ethical approval for this study (Ethical Committee No. 2010011052A.2) was provided by the Institutional Review Board (IRB) of National Cancer Institute-Cairo University, Cairo, Egypt (Chairperson Prof. Dr. Ahmed Morsi Mostafa) at 30/10/2011. This prospective randomized study was conducted on fifty urinary bladder cancer patients who were willing to participate and meet the following inclusion criteria: age 40–70 years old of both sex, ASA I and II undergoing radical cystectomy and urinary diversion in National Cancer Institute (NCI) from November 2011 till May 2012. Fully informed written consent was taken from each patient prior to contribution in the study. Exclusion criteria include hemodynamically unstable patients on vasopressors or inotropes, patients with contraindications to epidural catheter insertion, or patients' refusal. Lumbar epidural catheter is inserted at $L_{3/4}$ or $L_{4/5}$ intervertebral space preoperatively after detection of epidural space by loss of resistance technique and test dose of lidocaine 1% in epinephrine 1:200,000 is injected. Then patients were divided randomly by permuted block technique into two equal groups (twenty-five patients each): Group C (clonidine) and Group F (fentanyl).

Both groups received balanced general anesthesia (Midazolam 0.05 mg/kg, Fentanyl 2 μg/kg, Poropofol 2 mg/kg, Atracurium 0.5 mg/kg then 0.1 mg/kg every 30 min, Sevoflurane 1–2 MAC and Morphine 0.1 mg/kg IM + metoclopramide 10 mg IV) and activation of epidural analgesia is done immediately after complete recovery.

Group C (clonidine) includes twenty-five patients in whom activation of epidural analgesia is done using 6 ml of levobupivacaine (Chirocaine, 2.5 mg/ml, Abbott) 0.25% + clonidine (Catapress ampoule, 150 μg/ml, Boehringer Ingelheim) 75 μg bolus dose followed by continuous epidural infusion of levobupivacaine 0.125% + clonidine 2 μg/ml at a total rate of 6–10 ml/h according to VAS.

Group F (fentanyl) includes twenty-five patients in whom activation of the epidural is done using 6 ml of levobupivacaine (Chirocaine, 2.5 mg/ml, Abbott) 0.25% + fentanyl (Fentanyl ampoule, 50 μg/ml, Janssen Cilag) 50 μg bolus dose followed by continuous epidural infusion of levobupivacaine 0.125% + fentanyl 2 μg/ml at a rate of 6–10 ml/h according to VAS. A vial of paracetamol (Perfalgan, Bristol Myers Squibb) 1 g IV infusion over 20 min was given as rescue treatment analgesia with maximum dose of 3000 g/24 days although the maximum safe daily dose approved for paracetamol is 4000 g [29]. In both groups we measured vital signs (mainly heart rate, respiratory rate, and mean blood pressure) for 24 h, 0–10 visual analogue scale (VAS), Sedation using the four-points Ramsay Sedation Scale [30]: [0: awake and alert, 1: mildly sedated, easily aroused, 2: moderately sedated, aroused by shaking, 3: deeply sedated, difficult to be aroused by physical stimulation] were also assessed for the first 24 h postoperatively. Total dose of paracetamol IV infusion needed in both groups was calculated. In addition major side effects of the used drugs (e.g., respiratory depression, pruritis, nausea and vomiting) were observed and recorded.