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Original Contribution

Effect of the addition of clonidine to locally administered bupivacaine on acute and chronic postmastectomy pain☆,☆☆

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Abstract

Study Objectives: To investigate the analgesic effect of adding clonidine to topical bupivacaine for acute and chronic postmastectomy pain.

Design: Randomized, prospective, double-blinded study.

Setting: Cancer institute and university hospital.

Patients: 140 ASA physical status 1 and II women, aged 30 to 50 years, scheduled for modified radical mastectomy with axillary dissection for breast carcinoma.

Interventions: Patients were divided into 4 groups of 35 patients each, to receive either saline 0. 9% (control group), plain bupivacaine 0.5% (Bupivacaine group), plain bupivacaine 0.5% and 150 μg of clonidine (Clonidine150 group), or plain bupivacaine 0.5% and 250 μg of clonidine (Clonidine250 group). Study drugs were irrigated into the surgical field before skin closure.

Measurements and Main Results: Pain severity, time to first request of rescue analgesia, analgesic consumption, hemodynamics, and side effects were recorded in the first 48 hours postoperatively. The frequency of neuropathic pain was assessed using the Douleur Neuropathique 4-question survey (DN4) in the first and second postoperative months. Mean time to first postoperative analgesic request was significantly prolonged in the Bupivacaine (5.76 ± 0.85 hrs), Clonidine150 (11.6 ± 2.38 hrs), and Clonidine250 (17.4 ± 3.27 hrs) groups compared with the control group (1.86 ± 0.65 hrs). Postoperative tramadol consumption and visual analog scores (VAS) were significantly reduced in the Bupivacaine, Clonidine150, and Clonidine250 groups. Clonidine250 group patients had the lowest VAS scores from 2 to 48 hours postoperatively. Lower mean DN4 scores ($P = 0.000$) and a significantly reduced frequency of neuropathic pain ($P < 0.04$) were recorded in the Bupivacaine, Clonidine150, and Clonidine250 groups, with a nonsignificant difference noted among the treatment groups.

Conclusions: The addition of clonidine to topical bupivacaine accentuated its early postoperative analgesic efficacy.

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1. Introduction

Breast cancer is the most frequent neoplastic tumors in women, and surgical treatment is indicated in most patients [1]. Persistent pain with sensory disturbances following surgery is a significant clinical problem, with an average prevalence of 20% to 23.9% [2,3]. Postmastectomy chronic pain syndrome is defined as pain of neuropathic character located in the area of surgery and/or the ipsilateral arm, present at least 4 days per week, and with an average intensity of at least 3 on a 0-10 numeric rating scale [4]. The pathologic mechanisms may be related to patient characteristics, surgical technique, and adjuvant therapy [5]. Although the genesis of the pain is multifactorial, sectioning of the intercostobrachial nerve (a cutaneous branch of T1-T2) is the nerve lesion diagnosed most often [1].

Uncontrolled acute postoperative pain is defined as an important risk factor for the development of chronic pain [6]. Fassoulaki et al's analgesic regimen of local anesthetics and gabapentin is the most effective in preventing chronic postmastectomy pain [7]. Local anesthetics have been investigated in breast cancer patients through many routes: paravertebral blocks [8], thoracic epidurals [9], wound infiltration [10], topical lidocaine patch [11], and the topical application of eutectic mixture of local anesthetic (EMLA) cream applied to the operative site [12]. Most of above-cited studies suggested a better outcome in reduced postoperative pain and improved patient satisfaction.

Clonidine is an α2-adrenergic agonist that has been used as an adjunct to local anesthetics administered via different routes such as spinal [13], caudal, epidural [14], and peripheral nerve blocks [15]. The addition of clonidine enhanced the quality and duration of anesthesia, and accentuated postoperative analgesic efficacy [13-15]. The aim of this study was to investigate the effect of adding clonidine to locally instilled bupivacaine on acute postoperative pain after breast cancer surgery and on the possible development of chronic neuropathic pain.

2. Materials and methods

The study was approved by the Research Ethics Committee of the South Egypt Cancer Institute, Faculty of Medicine, Assiut University, Egypt. After obtaining an informed consent, 140 ASA physical status 1 and II women, aged 30-50 years, scheduled for modified radical mastectomy with axillary dissection for breast carcinoma, were enrolled in the study. Excluded from the study were patients with known allergy to study drugs; significant cardiac, respiratory, renal or hepatic disease; drug or alcohol abuse; body mass index (BMI) > 25 kg/m^2; or psychiatric illnesses that would interfere with perception and assessment of pain.

Using an online research randomizer (http://www.randomizer.org), patients were randomly allocated to 4 groups of 35 patients each, to receive either 15 mL of saline 0.9% (control group), 5 mL of plain bupivacaine 0.5% (Bupivacaine group), 5 mL of plain bupivacaine 0.5% and 150 μg of clonidine (Clonidine150 group), or 5 mL of plain bupivacaine 0.5% and 250 μg of clonidine (Clonidine250 group). Study drugs were diluted with saline 0.9% to 15 mL volume and irrigated into the surgical field before skin closure.

Preoperatively, patients were instructed in the use of the visual analog pain scale (VAS) score (0 = no pain to 10 = the worst pain imaginable). Patients received 5 mg of oral diazepam the night before surgery, and the anesthetic technique was standardized in all groups.

Anesthesia was induced with fentanyl 1.5 - 2 μg/kg, propofol 2 - 3 mg/kg, and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cisatracurium 0.15 mg/kg. Monitoring included electrocardiography, noninvasive blood pressure, pulse oximetry (SpO_2; %), and temperature. Anesthesia and muscle relaxation were maintained with isoflurane 1 - 1.5% minimum alveolar concentration in a 50% oxygen-air mixture. At the end of surgery but before skin closure, the study medications were irrigated into the wound with the drains clamped for 30 minutes. Muscle relaxation was reversed with neostigmine 50 μg/kg and atropine 20 μg/kg. Patients were extubated and transferred to the Postanesthesia Intensive Care Unit (PAICU).

PAICU data included heart rate (HR), noninvasive systolic (SBP) and diastolic blood pressure (DBP), respiratory rate (RR), and SpO_2, recorded immediately after surgery, and at 2, 4, 6, 12, 24, 36, and 48 hours postoperatively. Visual analog pain scores at rest (VAS.R) and during movement or ipsilateral arm abduction (VAS.M) were assessed at the same time points. Rescue analgesia consisting of intravenous (IV) tramadol 100 mg was given if requested or if VAS.R pain scores were ≥ 3. The time to first request of analgesia and total analgesic consumption in the first 48 hours were recorded. The patient's level of sedation was assessed at the same time points using a modified Observer's Assessment of Alertness/Sedation (OAA/S) scale (1 = awake/alert to 5 = sleep/unarousable). The attending anesthesiologist, surgeon, patient caregiver, and data collection personnel were blinded to patient group allocation.

Postoperative adverse effects such as nausea, vomiting, hypotension, bradycardia, tinnitus, convulsions, respiratory depression, and sedation were recorded and treated.

The probability of developing chronic neuropathic pain was assessed during regular postoperative examination in the Pain Clinic using the Douleur Neuropathique 4-question (DN4) survey [16] in the first and second postoperative months (Table 1).

2.1. Statistical analysis

The primary outcome measure was the total dose of analgesic consumed in the first 48 hours postoperatively. Secondary outcome measures were time to first request of rescue analgesic, postoperative VAS scores, hemodynamics,