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The Analgesic Effects of Incisional Levobupivacaine with Dexmedetomidine after Total Abdominal Hysterectomy

ORIGINAL INVESTIGATION

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ABSTRACT

Objective: The purpose of this study was to assess the analgesic efficacy of dexmedetomidine added levobupivacaine applied into the wound site by infiltration in total abdominal hysterectomy.

Materials and Methods: We studied 50 American Society of Anesthesiologists (ASA) physical status I–II patients scheduled for abdominal hysterectomy. The patients were randomized into two groups: infiltration of the surgical area with 0.25% levobupivacaine (40 mL) (Group L) or 0.25% levobupivacaine plus 2 mcg kg^{-1} dexmedetomidine (40 mL) (Group DL) 5 min before skin incision. After anesthesia induction, 5 min before surgical incision, 20 mL of the trial preparation (0.25% levobupivacaine or 0.25% levobupivacaine plus 2 mcg.kg^{-1} dexmedetomidine) was injected in the subcutaneus tissue along the marked line of skin incision. Another 20 mL of the same trial preparation was then infiltrated preperitoneally along the line of the planned incision of the peritoneum.

Results: Total meperidine consumption was significantly lower in Group DL (p=0.003). The visual analog scale (VAS) values at resting were significantly lower at 0, 2, and 4 h (p=0.001, 0.001, and 0.003, respectively) in Group DL in the postoperative period. VAS values at coughing were lower in Group DL at postoperative 0, 2, 4, 6, and 12 h (p=0.001; 001; 0.003; 0.006; 0.008 respectively). The need for rescue analgesic was significantly high in Group L (p<0.001).

Conclusion: Dexmedetomidine added to local anesthetic agent applied to the wound site reduced the analgesic consumption and improved the pain scores in total abdominal hysterectomy surgery.

Keywords: Dexmedetomidine, meperidine, postoperative analgesia, TAH

INTRODUCTION

Abdominal hysterectomy is associated with moderate to severe postoperative pain. To shorten the length of hospital stay and reduce the adverse effects of opioid agents, several methods of analgesia that have opioid-sparing effects are frequently used to reduce postoperative morbidity.

Levobupivacaine, a local anesthetic, is the pure S (-) enantiomer of racemic bupivacaine. It has significantly less cardiovascular (1) and central nervous system (2) toxicities. Infiltration of local anesthesia is an effective method for pain relief after many surgical procedures. In combination with general anesthesia, local anesthetic infiltration can reduce the analgesic consumption (3, 4).

Dexmedetomidine has a relatively high ratio of α_2/α_1; therefore, it is considered a full agonist of the α_2 receptor. It has sedative and analgesic sparing effects through the α_2 adrenoceptor in locus coeruleus. α_2 adrenoceptors are present in the peripheral and central nervous system at autonomic ganglia and presynaptic and postsynaptic sites. The activation of postsynaptic receptors in the central nervous system leads to the inhibition of sympathetic activity, decreases blood pressure and heart rate, and results in sedation. Binding of α_2 agonists to adrenoceptors in the spinal cord produces analgesia (5). There are several studies that have reported about the use of clonidine, an α_2 agonist, for postoperative analgesia as an infiltration agent (6-8). Dexmedetomidine has eight times stronger α_2 agonist effects than clonidine and there are studies asserting that the intravenous, intramuscular, intrathecal, epidural, and perineural use of this agent enhances the anesthetic and analgesic effects. However, its use in wound site infiltration has not been described.

We hypothesized that dexmedetomidine added to levobupivacaine infiltration for hysterectomy surgery has an opioid-sparing effect. The primary outcome measure in this study was 24 h meperidine hydrochloride consumption. The secondary outcome was VAS scores.

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MATERIALS and METHODS

In this prospective, randomized, double-blind, controlled study, after obtaining approval from the Ethics Committee (Karar no:2011/07) of our hospital and written informed consent from all patients, we studied 50 American Society of Anesthesiologists (ASA) physical status I–II patients scheduled for abdominal hysterectomy via a Pfannenstiel incision. The clinical trial is also registered with the clinical trial registry of the United States (www.clinicaltrial.gov) and the registration number for this trial is NCT01929252. The exclusion criteria were as follows: patients with second- or third-degree heart block, allergy to any study drug, renal insufficiency, hepatic insufficiency, psychiatric diseases, preoperative bradycardia (heart rate <45 beats/min), the use of α2 adrenergic agonists, a history of drug abuse, chronic pain, regular medication with analgesics, diabetes mellitus, ovarian cancer or endometrial cancer involving the myometrium, and a body mass index >30 kg/m^2.

Patients were randomized by sealed envelope method. In the operation room, the study solution (prepared by the second anesthesiologist in a sterile condition and in the same volume) was injected by the same surgeon who was blinded to the study solution. The person who prepared the study solution did not participate in data collection. In the operation room, standard monitoring was established. Heart rates, non-invasive blood pressures, and peripheral oxygen saturations were recorded. The hysterectomy was performed under general anesthesia, induced with 4–6 mg kg^{-1} intravenous thiopental and 2 mcg kg^{-1} fentanyl and 0.6 mg kg^{-1} rocuronium bromide. For maintenance, 2%–3% sevoflurane and 66% nitrous oxide in oxygen mixture at 6 L min^{-1} were used. NaCl (0.9%) was infused at a rate 5–10 mL kg^{-1} h^{-1}. In case of the heart rate being under 40 beats min^{-1}, 0.5 mg atropine sulfate was administered to the patients. All patients received 3 mg ondansetron at the beginning of the surgery. If the mean arterial blood pressure was less than 60 mm Hg, it was planned to administer 10 mg ephedrine. At the end of the surgery, residual neuromuscular block was reversed with neostigmine and atropine sulfate. Tracheal extubation was performed according to the standard criteria for extubation.

Infiltration of 0.25% levobupivacaine (40 mL) or 0.25% levobupivacaine plus 2 mcg kg^{-1} dexmedetomidine (40 mL) to the surgical area was performed to all patients 5 min before skin incision. The trial preparations were blinded and numbered. The infiltration technique was standardized: 5 min before surgical incision, 20 mL of the blinded trial preparation (0.25% levobupivacaine or 0.25% levobupivacaine plus 2 mcg kg^{-1} dexmedetomidine) was injected in the subcutaneous tissue along the marked line of skin incision. The other 20 mL of the same trial preparation was then infiltrated preperitoneally along the line of the planned incision of the peritoneum.

The patients' pain was evaluated with the visual analog scale (VAS, 0-10; 0=no pain, 10=maximum imaginable pain) as soon as they were responsive to verbal stimuli postoperatively. Postoperative pain was evaluated 0, 2, 4, 6, 12, and 24 h after extubation at rest and on cough. The patient-controlled analgesia (PCA) was initiated with meperidine. The PCA device (Abott Pain Management Provider, North Chicago, IL, USA) was programmed as 0.5 mg kg^{-1} loading dose, basal infusion rate 5 mg h^{-1}, bolus dose 5 mg kg^{-1}, and duration of lock out 15 min. The bolus dose was increased to 10 mg in patients with VAS >4. If it was not possible to provide an adequate level of analgesia, 75 mg diclofenac sodium was used as an additional analgesic. The Aldrete recovery score was evaluated for all patients (9). Nausea and vomiting was assessed by a four-point categorical scale (0=no nausea, 1=mild nausea, 2=severe nausea, 3=nausea leading to vomiting). Wound infection was evaluated in all cases.

Statistical analysis

The sample size was calculated on the basis of the power analysis. According to mean meperidine consumption in 10 patients in each group (Mean meperidine consumption in Group L=239.1±12.8 and 205.6±39.6 mg) at 95% significance level and 80% power, 23 patients were required in each group. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 15.0, SPSS, Inc, Chicago, IL, USA) software. The statistical analysis of the difference between the two groups with respect to age, weight, duration of surgery, recovery time, heart rate, mean arterial pressure, meperidine consumption, and VAS value was performed using an unpaired Student's t-test. Data on side effects were analysed with the chi-square test. A p value <0.05 was considered statistically significant.

RESULTS

Fifty patients were randomized to obtain the estimated sample size, and all patients completed the study (Figure 1).

Demographic characteristics were similar in both groups (Table 1). Surgery durations were also similar in both groups. There was no statistically significant difference with respect to the Aldrete recovery score ≥9 period between the two groups (Table 1). The number of patients who require rescue analgesic was significantly higher in Group L (Table 2). Total meperidine consumption was significantly lower in Group DL (Table 2). VAS values at rest were

Table 1. Demographic characteristics, duration of the surgery, and recovery times of the patients

	Group L (n=25)	Group LD (n=25)	p value
Age (years)	48.08±6.38	48.56±6.40	0.792
Weight (kg)	74.28±14.96	76.96±12.44	0.495
Surgical time (min)	88.6±14.27	84.84±17.84	0.415
Recovery time (min)	12.92±3.22	11.80±3.35	0.235

Table 2. Analgesic consumption of the groups

	Group L (n=25)	Group LD (n=25)	p value
Postoperative total meperidine consumption (mg/24 h)	232.88±13.98	210.24±33.33	0.003
Need for rescue analgesic agent (number)	23 (92%)	10 (40%)	<0.001

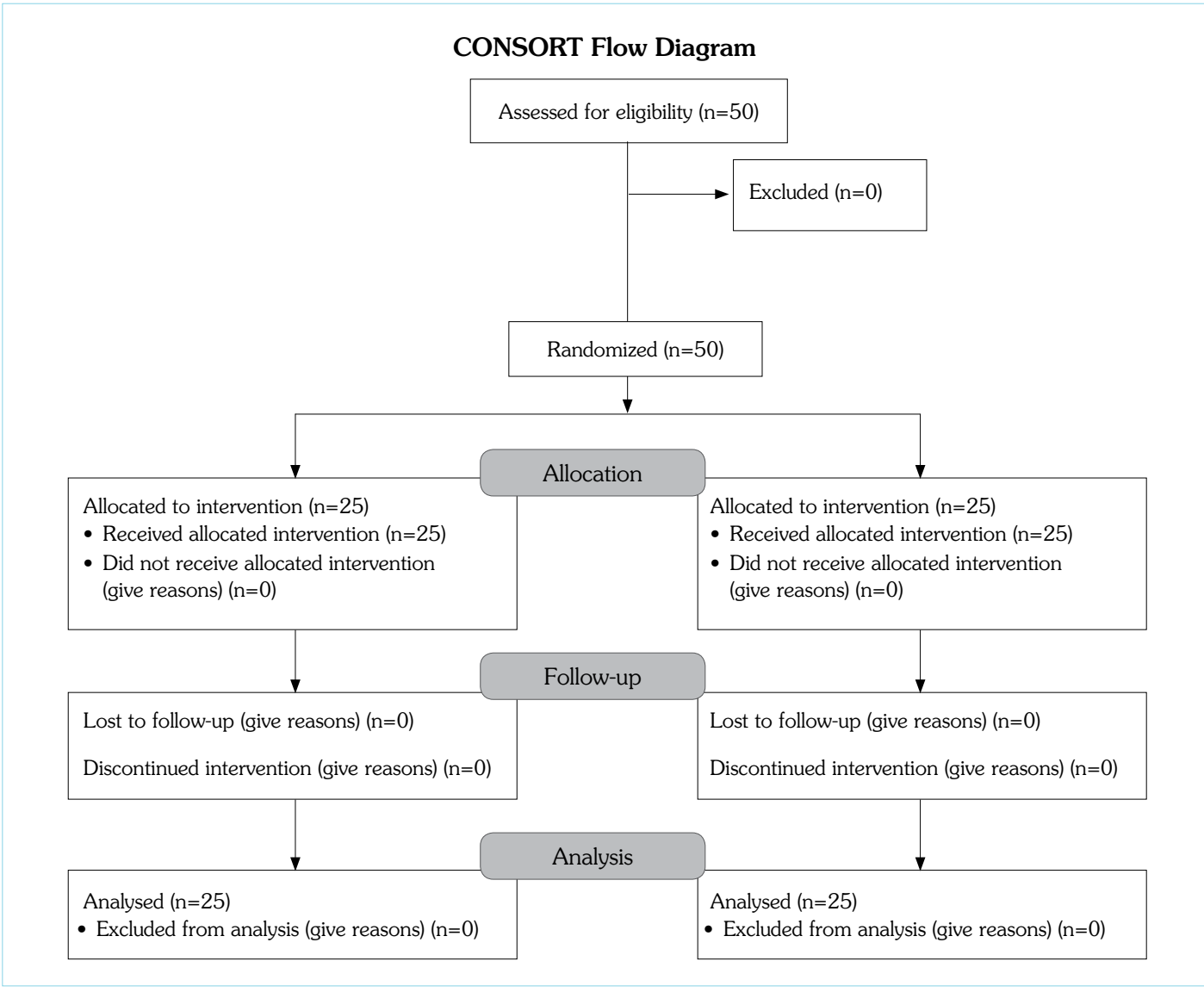

Figure 1. CONSORT diagram

less significant at 0, 2, and 4 h in Group DL (Figure 2). VAS values on coughing were less in Group DL at 0, 2, 4, 6, and 12 h (Figure 3). The mean arterial pressure and heart rate values were similar during the perioperative period and 2 h after operation (p=0.244). In Group L, two patients had mild nausea and one had vomiting, in Group DL, one patient had mild nausea and one patient had severe nausea. No other side effects were recorded. None of the patients developed wound site infection.

DISCUSSION

In this study, we demonstrated that 2 mcg kg^{-1} dexmedetomidine added to levobupivacaine for surgical wound infiltration reduced postoperative analgesic consumption and provided good postoperative VAS scores.

Surgical wound site infiltration is an effective method in pain management and various agents such as ephedrine, ketamine, ketorolac, opioid, and clonidine have been used in addition to local anesthetic agents to improve the analgesic effects (6-8, 10). Bhari et al. (6) compared the anesthetic effects of 30 mL of 0.25% bupivacaine alone and 3 mcg kg^{-1} clonidine added to bupivacaine as an intravenous or infiltration adjuvant, and they concluded that morphine consumption was reduced in both clonidine added groups and a better anesthetic effect was achieved by adding clonidine than only adding a local anesthetic agent. Giannoni (7) also mentioned in his study conducted on 60 tonsillectomy patients aged between 3 and 15 years that 1 mcg kg^{-1} clonidine added to ropivacaine infiltration reduced the fentanyl and codeine use and provided a faster return to daily activities.

There is no study assessing the use of dexmedetomidine in infiltration anesthesia. There are several studies asserting the positive effects of dexmedetomidine on postoperative pain by administering various methods. In 34 outpatient anesthesia patients, the first group received 0.4 mcg kg h^{-1} dexmedetomidine for 30 min before the end of surgery and was continued for 4 h postoperatively. The second group received 0.08 mg kg^{-1} morphine sulfate 30 min before the end of surgery, and it was concluded that the use of dex-

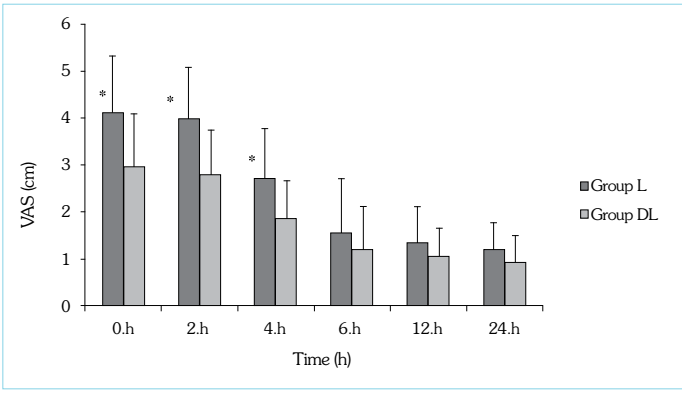

Figure 2. VAS values of the groups at rest

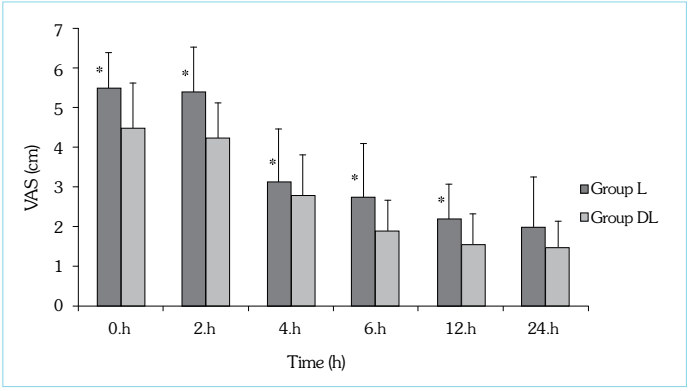

Figure 3. VAS values of the groups on coughing

medetomidine reduced postoperative morphine sulfate consumption by a rate of 66% (11). In a meta-analysis study conducted on 364 patients who underwent spinal anesthesia, it was stated that neuromuscular blockage duration, motor blockage duration, and the duration until first analgesic requirement was prolonged in case of intravenous dexmedetomidine administration. There was no statistically significant difference with respect to hypotension and postoperative sedation, and it was also stated that respiratory depression was not observed in any patient (12). In a study conducted on 30 patients who underwent hand surgery operation with regional intravenous anesthesia, it was reported that the addition of 0.5 mcg kg^{-1} dexmedetomidine to 40 mL of 0.5% lidocaine increased the quality of anesthesia (13). Esmaoglu et al. (14) reported that 100 mcg dexmedetomidine added to 40 mL of 5% levobupivacaine for perineural injection in axillary blockage shortened the blockage beginning time, increased the blockage duration and increased the postoperative analgesia duration. We also observed that adding 2 mcg kg^{-1} dexmedetomidine to levobupivacaine reduced the analgesic consumption for 24 h in patients who underwent abdominal hysterectomy. This effect could be mediated through the peripheral, central, and topical effects of dexmedetomidine.

It is not clear how α_2 agonists induce analgesia. It seems that they act in a central and peripheral manner. Peripherally α2 agonists inhibit the release of norepinephrine and also inhibit the action potential in the neuron. Centrally, at the level of the dorsal root ganglion, they inhibit the release of substance P, whereas they activate α_2 adrenoceptors in the locus ceruleus and produce analgesia (15, 16). The exact mechanism of the analgesic effects of topical dexmedetomidine is not well understood. It is stated that the sympathetic nervous system activity and norepinephrine release at the wound site have excitatory effects on nociceptive receptors (17). It is also a possible mechanism that dexmedetomidine inhibits the pain pathways at the wound site by inhibiting the prejunctional norepinephrine release. Furthermore, there are some studies asserting that dexmedetomidine exhibits peripheral analgesic effects by increasing the release of enkephalin-like materials and increases the effects of local anesthetics by selective blockage of conduction in Aδ and C fibers (18). In this study, dexmedetomidine may produce analgesia by central, peripheral, and topical mechanisms.

Abdullah et al. (12) reported that intravenous dexmedetomidine use did not result in sedation, hypotension, and respiratory depression in their meta-analysis that consisted of 364 spinal anesthesia patients. We also did not observe bradycardia or hypotension in any of our patients. There was no negative effect of dexmedetomidine on the postoperative recovery period.

The limitation of our study was that there was no group receiving dexmedetomidine by intravenous administration. In the presence of a group receiving dexmedetomidine by intravenous administration, the peripheral or central action mechanisms could be evaluated in more detail.

CONCLUSION

Dexmedetomidine added to the local anesthetic agent infiltrated to the wound site reduces the analgesic consumption and provides a better pain management. Further studies comparing the intravenous use of dexmedetomidine are necessary to address the effectiveness of the use of dexmedetomidine in wound site infiltration.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: AÜ, IG, İM Performed the experiments or case: İM Analyzed the data: AB, AÜ, FMK Wrote the paper: CB, AÜ. All authors have read and approved the final manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

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