ORIGINAL ARTICLE

# The effect of tramadol or clonidine added to intraperitoneal bupivacaine on postoperative pain in total abdominal hysterectomy

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## ABSTRACT

*Recent studies suggest that intraperitoneal application of local anesthetics is useful in abdominal surgery. Tramadol and clonidine have specific effects on peripheral nerves when used alone. We aimed to evaluate the effects of intraperitoneal application of bupivacaine and the combinations of bupivacaine plus tramadol and bupivacaine plus clonidine on postoperative pain in total abdominal hysterectomy.*

*After standard anesthetic procedure during closure of the abdomen, Group 1 (n = 20) was given 20 mL bupivacaine 0.5 percent, Group 2 (n = 20) was given 20 mL bupivacaine 0.5 percent plus 100 mg tramadol, and Group 3 (n = 20) was given 20 mL bupivacaine 0.5 percent plus 1 μg per kg clonidine, all into the peritoneal cavity. Postoperative pain was evaluated with the visual analog scale (VAS) at 30 minutes, and two, four, six, 12, and 24 hours after extubation. While patients were supine and seated, mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation ($SpO_2$) values were noted. When VAS scores were 4 to 7, 0.5 mg per kg of meperidine was given intramuscularly (IM); above 7, 1 mg per kg of meperidine was given IM; and when VAS scores were 2 to 4, 500 mg acetaminophen was given orally. For evaluating quality of analgesia, rescue analgesic dose, analgesia time, and side effects were noted.*

*The groups were similar in respect to $SpO_2$; however, when Group 1 was compared to Groups 2 and 3 at 30 minutes, and two, four, and six hours, MAP and HR measurements were found to be significantly higher ($p < 0.05$). VAS values in sitting and supine positions at 30 minutes and two hours were significantly lower in Group 2 ($p < 0.05$) when compared to Group 1. VAS values for Group 3 at 30 minutes, and two and four hours in the supine position, and at 30 minutes and two hours in the sitting position, were found to be significantly lower than those in Group 1 ($p < 0.05$). There were no significant differences between Groups 2 and 3.*

*The mean dosage of meperidine used was 76.7 ± 10.5 mg in Group 1, 63.9 ± 8.4 mg in Group 2, and 70 ± 5.2 mg in Group 3. When Group 1 was compared to Group 2, there were significant differences found ($p < 0.05$). First analgesic requirement time was found to be 30 (range, 30 to 30) minutes in Group 1, 120 (range, 30 to 240) minutes in Group 2, and 110 (range, 30 to 240) minutes in Group 3. There were significant differences found when Groups 2 and 3 were compared to Group 1 ($p < 0.05$).*

*We concluded that the combinations of bupivacaine plus tramadol and bupivacaine plus clonidine administered intraperitoneally in total abdominal hysterectomy operations provide more effective analgesia than bupivacaine alone during the early postoperative period.*

*Key words: postoperative analgesia, intraperitoneal administration, bupivacaine, tramadol, clonidine*

## INTRODUCTION

Postoperative pain is among the major problems encountered in surgical patients. When pain occurs, the patient finds it difficult to perform respiratory exercises and normal activities.[1] In the treatment of pain occurring after a surgical procedure, the goals should be to eliminate or reduce any discomfort that might be experienced by the patient, to facilitate the recovery process, and to avoid any side effects that might occur as a result of the treatment.

In 1991, Narchi et al. suggested intraperitoneal administration of local anesthetics after laparoscopy. When they administered the local anesthetic agents lidocaine and bupivacaine intraperitoneally, they found a reduction in

| Table 1. Demographic data of patients and duration of operation (mean ± SD) | | | |
|---|---|---|---|
| | **Group 1 (n = 20)** | **Group 2 (n = 20)** | **Group 3 (n = 20)** |
| Age (years) | 53.6 ± 12.7 | 51.8 ± 12.6 | 52.7 ± 9.3 |
| Weight (kg) | 74.8 ± 10.6 | 75.8 ± 9.6 | 73.9 ± 12.7 |
| Duration of operation (min) | 111 ± 19.6 | 112.6 ± 17.8 | 115 ± 11.76 |
| No statistically significant differences were found between the groups ($p > 0.05$). | | | |

postoperative pain as compared to the control group.[2-4] In contrast, some other investigators have found that intraperitoneal administration of bupivacaine or morphine is not an effective method.[5-7]

Tramadol is a weak opioid, selective for the μ receptors.[8] Recent studies suggest that tramadol may have specific local anesthetic properties on peripheral nerves when used alone.[9-11] As a result of these findings, the investigators thought that addition of tramadol to local anesthetic would be effective.

Clonidine has depressant properties on the C-fiber action potential and produces tonic and phasic inhibition of nerve conduction in vitro.[12] As an adjunct, clonidine showed an enhancing effect on lidocaine-induced inhibition of C-fiber action potential.[13]

In our study, we aimed to evaluate how bupivacaine, a combination of bupivacaine plus tramadol, and a combination of bupivacaine plus clonidine, affected postoperative pain, analgesic consumption, and vital signs when administered intraperitoneally in total abdominal hysterectomy operations.

## MATERIALS AND METHODS

After approval granted by the Hospital Ethical Committee, our study was conducted on 60 patients who were scheduled for total abdominal hysterectomy with an American Society of Anaesthesiologists (ASA) status of ASA I or ASA II, and who had no history of allergy to local anesthetic and opioid agents. Exclusion criteria were known allergy or contraindications to anesthetics or any drug used, asthma, renal insufficiency, cardiac disease, relative hypovolemia or such as from dehydration, and history of allergy to local anesthetic and opioid agents.

The patients were randomized to three groups of 20 each. The study design was randomized and double-blinded. Identical syringes containing each drug were prepared by an anesthesiology assistant not involved in the study according to the randomization list that was generated. As premedication, midazolam 0.15 mg per kg and atropine 0.01 mg per kg were administered intramuscularly (IM) 45 minutes before the surgical procedure. Anesthesia was induced by administering thiopental sodium 5 mg per kg intravenously (IV) and was maintained by 50 percent $O_2$, 50 percent $N_2O$, and 1 to 1.5 percent isoflurane after intubation had been achieved with atracurium 0.5 mg per kg. After the induction of anesthesia, all patients were administered an IV injection of fentanyl 2 μg per kg and 8 mg IV ondansetron for postoperative nausea or vomiting. Muscle relaxation was maintained by IV administration of atracurium 0.2 mg per kg. No other opioid analgesics were used during the operation. The 20 patients assigned to Group 1 received 20 mL of bupivacaine 0.5 percent; the 20 patients assigned to Group 2 received 20 mL of bupivacaine 0.5 percent plus tramadol 100 mg; and the remaining 20 patients assigned to Group 3 received 20 mL of bupivacaine 0.5 percent plus clonidine 1 μg per kg, all administered to the peritoneal cavity. MAP, $SpO_2$, and HR values were recorded 30 minutes after extubation and at two, four, six, 12, and 24 hours.

Assessment of postoperative pain when lying down and on movement (by putting the patient in a sitting position) was made on the basis of the visual analog scale (VAS), where 0 = "no pain" and 10 = "worst pain imaginable." VAS measurements were taken 30 minutes after extubation and at two, four, six, 12, and 24 hours. Patients who had a postoperative pain score of 4 to 7 were administered IM meperidine 0.5 mg per kg. Those who had a postoperative pain score of 7 or higher were administered IM meperidine 1 mg per kg. Total amounts of meperidine administered to each group were recorded. Patients who had a postoperative pain score of 2 to 4 were given oral acetaminophen 500 mg, and total amounts of acetaminophen received by each group were recorded. These measurements were recorded by an anesthesiology resident who did not know which medication was administered. Measurements in all patients were performed by the same person.

In our study, pain scores were used to determine analgesic effectiveness. To get information on the quality of analgesia, additional analgesics needed by each group within 24 hours and time to analgesic need were determined. Analgesic need was regarded as the time elapsed between the administration of the study agent and the administration of an additional analgesic.

Nausea and vomiting were assessed on a 4-point scale (0 = no nausea/vomiting; 1 = nausea alone; 2 = moderate vomiting; 3 = severe vomiting). Degree of sedation was measured on a 3-point scale (0 = alert; 1 = drowsy but arousable to voice; 2 = very drowsy, arousable to shaking). These assessments were recorded 30 minutes after extubation and at two, four, six, 12, and 24 hours.

| Table 2. Visual analog scale (VAS) scores of pain at rest and in motion | | | | | | |
|---|---|---|---|---|---|---|
| Time | VAS - supine position | | | VAS - sitting position | | |
| | Group 1 | Group 2 | Group 3 | Group 1 | Group 2 | Group 3 |
| 30 minutes | 7 (6 – 10) | 2 (1 – 5)* | 5 (0 – 6)* | 8 (7 – 10) | 3 (2 – 6)* | 6 (1 – 8)* |
| 2 hours | 7 (0 – 8) | 3 (1 – 7)* | 4 (2 – 7)* | 8 (1 – 8) | 4 (2 – 5)* | 6 (3 – 8)* |
| 4 hours | 5 (2 – 9) | 4 (2 – 5) | 3 (1 – 7)* | 6 (3 – 10) | 5 (2 – 6) | 4 (2 – 8) |
| 6 hours | 4 (1 – 7) | 2 (1 – 4) | 3 (1 – 6) | 4 (2 – 8) | 3 (2 – 5) | 4 (2 – 7) |
| 12 hours | 2 (2 – 5) | 2 (1 – 3) | 2 (1 – 4) | 3 (2 – 5) | 3 (1 – 4) | 3 (1 – 4) |
| 24 hours | 1 (1 – 3) | 1 (0 – 2) | 1 (0 – 3) | 2 (2 – 3) | 2 (2 – 3) | 3 (1 – 4) |
| Values are median, range appears in parentheses. n = 20 for each group. *p < 0.05 when compared to Group 1. | | | | | | |

## STATISTICAL ANALYSIS

Prestudy power analysis determined a sample size of 20 patients per group as having an 80 percent chance (ß = 0.20) for detecting a 34-mg difference in rescue meperidine requirements during the first 24 hours after surgery at the 95 percent confidence interval limitations (ß = 0.05).[14]

The Mann-Whitney U test was used to analyze the demographic data related to the patients. MAP, HR, $SpO_2$, and postoperative meperidine and acetaminophen administration data were analyzed using the One-Way ANOVA test. The Tamhane posthoc test was applied to determine the significance of differences in means because of nonhomogeneous variance of groups. VAS and the first analgesic requirement time were analyzed by using the Kruskal-Wallis test. If a significant result was obtained, the Bonferroni posthoc test was performed for multiple comparisons. The Chi-square (Fisher's exact) test was used for evaluating adverse events. These values were represented as the arithmetic mean and standard deviation (mean ± SD). Levels of significance were determined as $p < 0.05$ for significant difference.

## RESULTS

Table I shows the demographic characteristics of the patients. No statistically significant differences were found between the groups ($p > 0.05$).

VAS values in Groups 1 and 2 were compared while the patients were in sitting and supine positions; it was determined that at 30 minutes and two hours the pain scores were significantly lower in Group 2 ($p < 0.05$). Pain scores measured with patients in the supine position in Groups 1 and 3 at 30 minutes, two hours, and four hours, and at 30 minutes and two hours with patients in the sitting position were found to be significantly lower in Group 3 ($p < 0.05$). There was no significant difference when Groups 2 and 3 were compared (Table 2).

The mean dosage of meperidine used was 76.7 ± 10.5 mg in Group 1, 63.9 ± 8.4 mg in Group 2, and 70 ± 5.2 mg in Group 3. When Group 1 was compared to Group 2, there were statistically significant differences found ($p < 0.05$). There were no statistically significant differences between other groups. Acetaminophen use was 500 mg in Groups 1, 2, and 3, with no difference between the groups ($p > 0.05$).

First analgesic requirement time was found to be 30 minutes (range, 30 to 30) in Group 1, 120 minutes (range, 30 to 240) in Group 2, and 110 minutes (range, 30 to 240) in Group 3. When Group 1 was compared to Groups 2 and 3, there were significant differences found ($p < 0.05$). When Groups 2 and 3 were compared, there were no statistically significant differences.

When the groups were compared for MAP, HR, and $SpO_2$ values during the postoperative period, no significant differences were found for $SpO_2$ ($p > 0.05$). Comparison of MAP and HR measurements in Group 1 to those of Groups 2 and 3 at 30 minutes, two hours, four hours, and six hours, however, found them to be significantly high ($p < 0.001$). When Groups 2 and 3 were compared, there were no statistically significant differences ($p > 0.05$) (Table 3).

One patient in Group 1, two patients in Group 2, and one patient in Group 3 experienced postoperative nausea rated 1 in severity and requiring no treatment. No statistically significant differences were found ($p > 0.05$). No sedation was seen in all patients.

## DISCUSSION

In our study, we demonstrated that the combinations

**Table 3. Changes of mean arterial pressure, heart rate, and peripheral oxygen saturation (mean ± SD)**

| Time | MAP | | | HR | | | $SpO_2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 1 | Group 2 | Group 3 | Group 1 | Group 2 | Group 3 |
| 30 minutes | 107 ± 7.7 | 81.8 ± 7.3* | 82.6 ± 9.9* | 102 ± 6.7 | 76.8 ± 4.3* | 77.6 ± 8.9* | 98.6 ± 0.48 | 98.6 ± 0.5 | 98.7 ± 0.48 |
| 2 hours | 103.2 ± 5.1 | 85.4 ± 7.0 | 82.1 ± 4.3* | 98.2 ± 5.2 | 80.4 ± 6.0* | 77.1 ± 5.3* | 98.5 ± 0.5 | 98.6 ± 0.5 | 98.6 ± 0.4 |
| 4 hours | 95.2 ± 8.9 | 86.2 ± 4.6* | 81.5 ± 9.8* | 90.2 ± 3.9 | 81.2 ± 4.6* | 76.5 ± 6.8* | 98.6 ± 0.5 | 98.8 ± 0.5 | 98.6 ± 0.5 |
| 6 hours | 97.4 ± 6.2 | 82.1 ± 6.1* | 83.9 ± 5.6* | 92.4 ± 4.2 | 77.1 ± 6.1* | 78.4 ± 3.6* | 98.5 ± 0.5 | 98.8 ± 0.6 | 98.5 ± 0.5 |
| 12 hours | 88.2 ± 4.0 | 89.6 ± 7.1 | 88.6 ± 5.5 | 80.2 ± 4.07 | 79.6 ± 6.1 | 78.6 ± 5.7 | 98.7 ± 0.5 | 98.8 ± 0.7 | 98.6 ± 0.5 |
| 24 hours | 89.7 ± 3.5 | 90.1 ± 4.3 | 88.6 ± 6.7 | 81.7 ± 3.5 | 79.1 ± 4.3 | 78.6 ± 4.9 | 98.8 ± 0.4 | 98.8 ± 0.6 | 98.8 ± 0.4 |

MAP (mmHg), mean arterial pressure; HR (beats/minute), heart rate; $SpO_2$ (percent), peripheral oxygen saturation. n = 20 for each group. * $p < 0.05$ when compared to Group 1.

of bupivacaine plus tramadol and bupivacaine plus clonidine, administered intraperitoneally in total hysterectomy operations, provide more effective analgesia than bupivacaine alone during the early postoperative period.

Tramadol has a dual mechanism of action, also blocking the reuptake of the norepinephrine and 5-hydroxy-tryptamine at the α2-adrenergic receptor level.[15,16] The pretreatment with α-adrenoreceptor antagonists yohimbine and idazoxan caused a significant reduction of tramadol's antinociceptive effect.[17] As a result, tramadol has a profile of action similar to that of clonidine, which inhibits the release of norepinephrine from prejunctional α2-adrenoreceptors in the periphery.[18] In view of this hypothesis, we compared the effect of addition of tramadol and clonidine to local anesthetic in our study. During our literature search, we did not find any study of intraperitoneal local anesthetics and intraperitoneal opioids administered to patients who underwent an open lower abdominal operation, which would be considered similar to our study. Kapral et al. obtained a prolongation of the motor blockade of the brachial plexus with 100 mg tramadol added to mepivacaine.[10] Acalovschi et al. found that 100 mg tramadol provided a shorter onset time of sensory block in intravenous regional anesthesia.[16] In our study, we used a similar dose of 100 mg tramadol.

In different studies, addition of clonidine to local anesthetic was investigated. Culebras et al. determined that addition of 150 μg clonidine to local anesthetic did not prolong the interscalene block,[19] whereas other investigations in regional anesthesia determined that addition of clonidine improved the effects of local anesthetics.[20-23] Singelyn et al.[20] added 30 μg clonidine to mepivacaine in a brachial plexus block, Bernard et al.[21] added 0.5 μg per kg clonidine to lidocaine in a brachial plexus block, Tschernko et al.[22] added 2 μg per kg clonidine to bupivacaine in an intercostal nerve block, and Joshi et al.[23] added 1 μg per kg clonidine to intra-articular bupivacaine—all of these improved analgesia of the local anesthetics. In our study, we used a similar dose of clonidine at 1 μg per kg.

Ali et al. administered 20 mL of bupivacaine 0.5 percent and 20 mL of lidocaine 2 percent together with epinephrine intraperitoneally to patients undergoing total abdominal hysterectomy,[24] and Williamson et al. administered a total amount of 200 mg of lidocaine in 50 mL saline intraperitoneally together with adrenaline to patients undergoing total abdominal hysterectomy.[25] When both groups of investigators evaluated the need for analgesia during the postoperative period and compared the use of morphine with the control group, they concluded that intraperitoneal administration of local anesthetics had no effect. We found similar results to Ali et al. in that 20 mL of bupivacaine 0.5 percent had no postoperative

analgesic effect alone in patients undergoing total abdominal hysterectomy. Bupivacaine was selected because it is the most widely used local anesthetic in our country.

Pang et al. injected 25 mg tramadol IM and demonstrated that it has local anesthetic effect.[9] Clonidine has also been reported to depress nerve action potentials, especially in C fibers, by a mechanism independent of the stimulation of α2-adrenergic receptors.[12,13] This mechanism accounts for strengthening of the local anesthetic block achieved by perineal administration of the drug. Finally, α2-adrenergic receptors located at nerve endings may play a role in the analgesic effect of the drug by preventing norepinephrine release.[26,27] In another study, results revealed that clonidine and, much more potently, dexmedetomidine inhibit peristalsis of the guinea pig ileum. The inhibition is caused by interaction with α2-adrenoceptors and, in the case of clonidine, also involves activation of small conductance $Ca^{2+}$-activated potassium channels and endogenous opioidergic pathways.[28] In our study, we considered that tramadol (a low-potency opioid) and clonidine (an α2 agonist), with their local anesthetic effect, would increase the effect of bupivacaine and delay the onset of the pain, while also reducing its severity. Systemic absorption may have played a role, but it has been demonstrated that local intraperitoneal bupivacaine and intraperitoneal meperidine were better than the combination of intraperitoneal bupivacaine and IM meperidine for postoperative analgesia in patients undergoing laparoscopic tubal ligation, demonstrating a local effect.[29]

The most frequent side effect of tramadol is nausea and vomiting; hemodynamic and respiratory depression are rarely seen.[30,31] The most common side effect of clonidine is hypotension, and there are studies on clonidine's transmission to the heart, which causes dangerous rhythm defects.[32,33] We did not see side effects other than nausea in our study groups; this may be because of our having used prophylactic ondansetron.

The most important complication of intraperitoneal local anesthetic application is IV injection. With sudden increase of systemic absorption, toxic symptoms can be seen. Intraperitoneally administered opioids cause constipation and ileus by affecting μ receptors in the gastrointestinal tract. Incidence of infection is rare because of widespread antimicrobial action of local anesthetics.[34]

Pain increases sympathetic activity, which causes tachycardia, an increase in peripheral vascular resistance, and, related to this, an increase in the workload of the heart.[35] Comparing Group 1 to Groups 2 and 3, the increase in MAP and HR is associated with increase in sympathetic activity.

We conclude that the combinations of bupivacaine plus tramadol and bupivacaine plus clonidine administered intraperitoneally in total hysterectomy operations provide more effective analgesia than bupivacaine alone during the early postoperative period.

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