The addition of droperidol or clonidine to epidural tramadol shortens onset time and increases duration of postoperative analgesia

[L'addition de dropéridol ou de clonidine à l'administration péridurale de tramadol raccourcit le délai d'installation et prolonge la durée de l'analgésie postopératoire]

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Purpose: To compare tramadol alone and the combinations of either tramadol-clonidine or tramadol-droperidol with regard to analgesic and adverse effects.

Methods: After Ethic's Committee approval and patient informed consent were obtained, epidural catheters were inserted preoperatively at the L_{3-4} interspace in 90 ASA physical status I–II adult patients undergoing lower abdominal surgery. Anesthesia was standardized. Patients were randomly assigned to one of three groups. Group I (T) patients received tramadol 75 mg, Group II (TD) patients received tramadol 75 mg plus droperidol 2.5 mg, and Group III (TC) patients received tramadol 75 mg plus clonidine 150 μg in a total volume of 10 mL administered as a single epidural injection in the postanesthesia care unit. The onset time of analgesia and duration of analgesia, visual analogue pain scores, sedation, nausea scores, vital signs and side effects were recorded.

Results: Duration of analgesia was similar in both the TD and TC groups, and significantly longer than in the T group ($P < 0.001$). Group TC patients displayed a significant increase in sedation scores and decrease in blood pressure and heart rate when compared with other groups ($P < 0.001$). No adverse effects were observed in Group TD, while nausea scores were high in both the T and TC groups ($P < 0.001$). Pain score, respiration rate, and SpO_2 values were similar in all study groups.

Conclusion: We conclude that epidural tramadol in combination with droperidol or clonidine prolongs the duration of analgesia; however, droperidol appears to be a better alternative when adverse effects and antiemetic properties are taken into consideration.

Objectif : *Comparer le tramadol à la combinaison de tramadol-clonidine ou de tramadol-dropéridol en regard de leurs effets analgésiques et indésirables.*

Méthode : *Ayant obtenu l'approbation du Comité d'éthique et le consentement éclairé des patients, nous avons réalisé l'insertion préopératoire d'un cathéter péridural dans l'espace intercostal L_{3-4} chez 90 patients adultes d'état physique ASA I–II devant subir une intervention abdominale basse. L'anesthésie a été normalisée. Les patients ont été répartis en trois groupes de façon aléatoire. Ceux du groupe I (T) ont reçu 75 mg de tramadol, ceux du groupe II (TD), 75 mg de tramadol et 2,5 mg de dropéridol et du groupe III (TC), 75 mg de tramadol plus 150 μg de clonidine dans un volume total de 10 mL administré à la salle de réveil en une seule injection péridurale. Le délai d'installation et la durée de l'analgésie, la douleur selon l'échelle visuelle analogique, la sédation, les nausées, les signes vitaux et les effets secondaires ont été notés.*

Résultats : *La durée de l'analgésie a été comparable entre les groupes TD et TC et significativement plus longue que dans le groupe T ($P < 0,001$). Les patients du groupe TC, comparés à ceux des autres groupes, ont connu une hausse significative des scores de sédation et une baisse de la tension artérielle et de la fréquence cardiaque ($P < 0,001$). Aucun effet indésirable n'a été observé dans le groupe TD tandis que les scores de nausées ont été plus élevés dans les groupes T et TC ($P < 0,001$). Les scores de douleur, la fréquence respiratoire et la SpO_2 ont présenté des valeurs similaires dans tous les groupes de l'étude.*

Conclusion : *Nous pouvons conclure que l'administration péridurale de tramadol, combinée au dropéridol ou à la clonidine, prolonge la durée de l'analgésie ; cependant, le dropéridol semble un meilleur choix quand on considère les effets indésirables et les propriétés antiémétiques.*

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EPIDURAL opioid administration is one of the most common techniques for postoperative pain control. Epidural administration of low dose opioids provides strong and long lasting segmental analgesia via opioid receptors.[1] However, the known adverse effects of epidural opioids require a very careful selection of the agent and dosage. Although epidural morphine, fentanyl, alfentanil and pethidine provide effective analgesia and are associated with a low systemic redistribution, the risk of respiratory depression increases with repeated and continuous administration of epidural opioids. Tramadol may be advantageous because of a low risk of respiratory depression.[2,3] Tramadol is a weak agonist at all types of opioid receptors with some selectivity for μ receptors. Also, tramadol inhibits the reuptake of norepinephrine and serotonin, thus increasing the concentrations of these two neurotransmitters in the central nervous system.

In clinical studies, spinal or epidural administration of non-opioid agents such as clonidine, droperidol, neostigmine, ketamine, midazolam, somatostatine and calcitonin have been shown to provide analgesia without causing motor dysfunction or neurotoxicity.[4–8] Epidural droperidol blocks mainly the fast, and to a lesser extent, the slow sodium channels and inhibits the formation of action potential. Clonidine, which is an alpha$_2$ adrenergic agonist, has an anti-nociceptive effect on a wide dynamic range of neurons and δ receptors. Although they cannot provide sufficient analgesia by themselves, when used as adjuncts to low-dose opioids, they decrease adverse effects, and increase the quality and duration of analgesia.[9–14]

At present, there is no ideal drug or combination of drugs for postoperative epidural analgesia. The present study was conducted to compare the analgesic and adverse effects (sedation, nausea, vomiting and hemodynamic changes) of epidural tramadol used alone, and the combinations of tramadol-droperidol and tramadol-clonidine.

Methods

After obtaining approval from the local Ethics Committee and written informed consent, 90 patients aged 20–68 yr, ASA physical status I and II, scheduled for elective total abdominal hysterectomy, were selected for this prospective, randomized and double-blind study. Randomization was performed by using computer generated random numbers, kept in consecutively numbered and sealed envelopes. Exclusion criteria were a history of cardiovascular, respiratory, or central nervous system diseases, bleeding disorders, use of opioids and drugs that affect the central nervous system (mono amine oxydase inhibitors, carbamazepine, quinidine and cimetidine), difficulty of cooperation and pregnant patients.

TABLE I Sedation scores[15]

0	Alert or drowsy but easily aroused to an alert state by verbal commands alone
1	Sleeping and arousable by verbal commands
2	Sleeping and not aroused by verbal stimuli, but aroused to a drowsy state by tactile stimulation
3	Sleeping and not aroused to a drowsy state by tactile stimulation

TABLE II Nausea and vomiting scores[16]

0	No nausea/vomiting
1	Mild nausea/vomiting (patient not requesting an antiemetic)
2	Nausea/vomiting patient requesting an antiemetic
3	Nausea/vomiting, resistant to antiemetic

TABLE III Demographic data and duration of surgery (mean ± SD)

	T (n = 30)	*TD (n = 30)*	*TC(n = 30)*
Age (year)	53.8 ± 9.4	51.3 ± 9.1	52.3 ± 8.9
Body weight (kg)	64.5 ± 10.8	63.5 ± 10.5	64.7 ± 11.0
Length (cm)	162.4 ± 12.4	160.2 ± 11.9	164.1 ± 12.0
Sex (M/F)	14/16	12/18	15/15
ASA (I/II)	30/0	28/2	28/2
Duration of surgery (min)	92.5 ± 9.0	91.9 ± 8.8	92.7 ± 9.3

T = tramadol alone; TD = tramadol-droperidol; TC = tramadol-clonidine.

All patients were taken into the operating room unpremedicated. After standard monitoring with non-invasive blood pressure, electrocardiography and peripheral oxygen saturation (SpO_2), administration of Lactated Ringer's solution was started. Patients were positioned in the lateral decubitus and a 20-G epidural catheter (Perifix 401, B.Braun, Melsungen AG) was inserted through an 18-gauge Tuohy needle at the $L_{3–4}$ interspace. The same anesthesiologist (E.G.) inserted all epidural catheters. After injection of 2 mL 0.5% bupivacaine with 15 μg adrenalin through the epidural catheter as a test dose, the catheter was fixed and the patient was repositioned supine. Induction of anesthesia was achieved with propofol (2 mg·kg^{-1}) and cis-atracurium (0.2 mg·kg^{-1}). The trachea was intubated and the lungs ventilated mechanically. Anesthesia was maintained with an O_2/N_2O mixture (50%:50%), isoflurane and cis-atracurium.

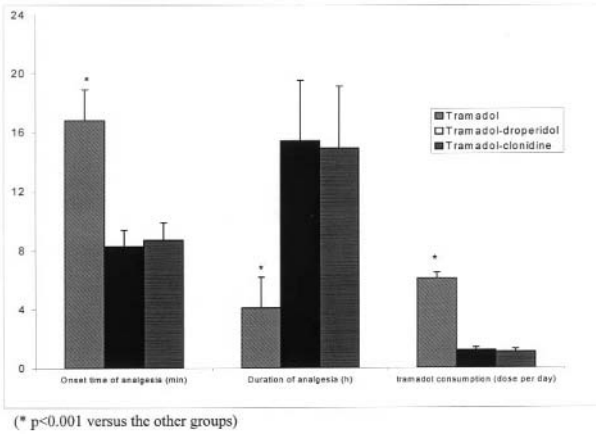

FIGURE 1 Onset time and duration of analgesia and tramadol consumption in number of doses required in 24 hr.

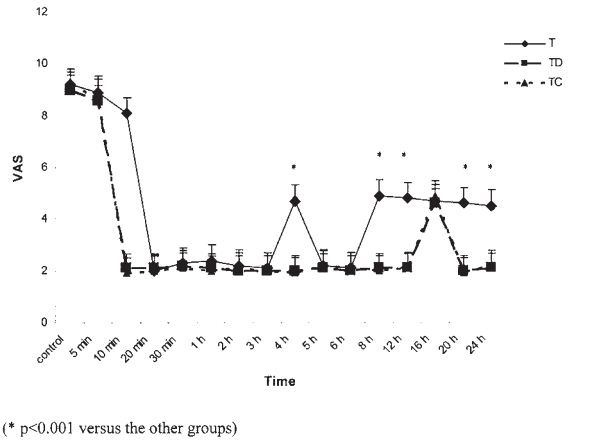

FIGURE 2 Visual analogue scale (VAS) after surgery.

After surgery, patients were admitted to the postanesthetic care unit. They were randomly assigned to one of three groups when they stated having pain and were hemodynamically stable. Group I (T) patients received tramadol 75 mg, Group II (TD) received 75 mg tramadol plus 2.5 mg droperidol, and Group III (TC) received 75 mg tramadol plus 150 µg clonidine in a total volume of 10 mL administered as a single epidural injection by an investigator blinded to study group.

The intensity of postoperative pain was measured with the visual analogue scale (VAS). Sedation was monitored on a four-point scale (Table I)[15] and nausea was monitored on a four-point scale (Table II).[16] The onset time of analgesia, duration of analgesia and total tramadol dose were recorded. The onset time of analgesia was defined as the time required to decrease the VAS score control value by 20 mm, and duration of analgesia as the increase of VAS score value by 20 mm. The need for additional tramadol or TC/TD was defined as an increase in the VAS pain score of 20 mm or more. Total tramadol consumption during the last 24 hr is reported in all patients. Vital signs (respiratory rate, SpO_2, heart rate, blood pressure), sedation and nausea scores, VAS pain scores and adverse effects were assessed before injection, and at five, ten, 20, 30 min, one, two, three, four, five, six, eight, 12, 16, 20, and 24 hr after epidural injection. In cases of VAS scores 5 cm at rest 30 min after epidural injection, patients were given 1 $mg \cdot kg^{-1}$ meperidine *im*. When nausea and vomiting were ≥ 2, patients were given metoclopramide 10 mg *iv*. Hypotension, defined as a reduction of the systolic blood pressure > 20%, was treated with the rapid infusion of lactated Ringer's solution and *iv* boluses of ephedrine. All postoperative assessments were made by an investigator blinded to study group.

Previous studies have determined that the effective dose of epidural tramadol for postoperative analgesia ranges from 75 to 200 mg. With a level of α 0.05 and ß level of 0.2, power analysis indicated that 30 observations would be needed to detect clinically relevant differences in tramadol consumption. A 50% decrease in the tramadol consumption in the treatment groups would be of clinically relevance.[17] Intergroup comparison of demographic data was made by Student's t test. The three groups were compared by Mann Whitney U test for non-parametric data. Comparison was made by one-way analysis of variance (ANOVA) followed by a Student's t test for parametric data. Results were expressed as mean ± standard deviation. A value of $P < 0.05$ was considered statistically significant.

Results

The three groups of patients were similar with respect to demographic data, ASA physical status and duration of surgery (Table III). The onset time of analgesia was 16.8 ± 2.1 min, 8.3 ± 1.1 min, and 8.7 ± 1.2 min in the T, TD, and TC groups, respectively. It was longer in the T group than in the TD and TC groups ($P < 0.001$). Patients in the T group displayed shorter durations of analgesia than in the other groups (4.1 ± 2.1 hr, 15.4 ± 4.1 hr, and 14.9 ± 4.2 hr in T, TD,

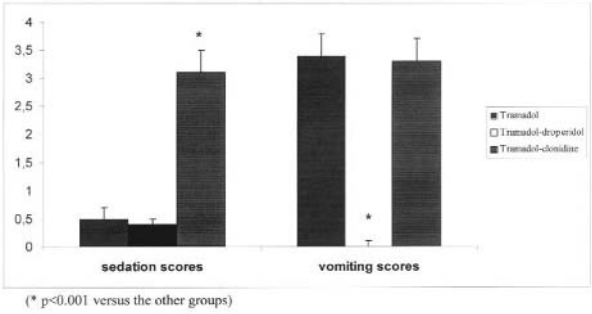

FIGURE 3 Sedation and nausea/vomiting scores ten minutes after epidural injection.

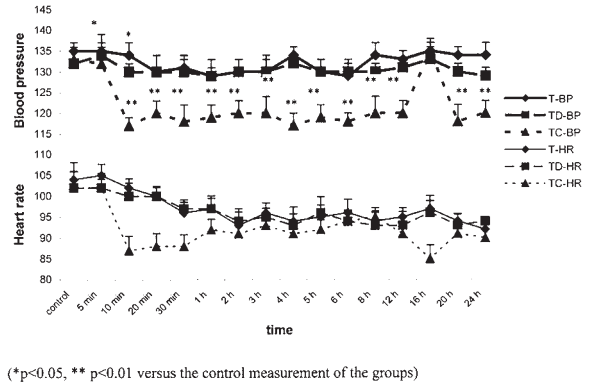

FIGURE 4 Systolic blood pressure and heart rate in the postoperative period (mean ± SD).

and TC groups respectively; $P < 0.001$). Tramadol consumption (doses per day) was higher in the T group than in the TD and TC groups ($P < 0.001$). Tramadol consumption was 457.5 ± 16.7 mg, 90 ± 8.2 mg, and 82.5 ± 8.9 mg in the T, TD and TC groups respectively (Figure 1).

VAS pain scores in the T group were significantly higher when compared with the other groups at four, eight, 12, 20 and 24 hr ($P < 0.001$). No difference was found for the VAS score at the 16th hr. No patient required meperidine (Figure 2).

Group T and TD patients did not show any sedation, however group TC patients had increased sedation scores at ten minutes (Figure 3; $P < 0.001$). Patients in the T and TC groups had higher nausea scores than those in the TD group at ten minutes ($P < 0.001$; Figure 3). There was no statistical significant difference for nausea/vomiting and sedation scores at the other time points. The incidence of nausea and vomiting ten minutes after epidural injection was 24%, 0.1%, and 22% in the T, TD and TC groups respectively. Six patients in the T group and seven patients in the TC group received metoclopramide for nausea and vomiting.

Blood pressure and heart rate were not different from control in the T and TD groups. Patients in the TC group showed a decrease of 10% ($P < 0.01$) in blood pressure and of 6% ($P < 0.05$) in heart rate beginning ten minutes after injection until the end of the study (Figure 4). Respiratory rate and SpO_2 values were within normal ranges in all patients.

Discussion

Mean onset time of analgesia has been reported as 10–15 min for epidural tramadol and 5–11 min for the tramadol-droperidol combination.[2,16,18] Furthermore, it has been stated that a combination of clonidine with fentanyl, sufentanil and morphine decreases the onset time of analgesia by 50%.[4,19,20] Consistent with previous reports, the present study shows that the onset time of analgesia was 16 min time with tramadol alone and that this time decreased to approximately eight minutes when either clonidine or droperidol was added.

The mean durations of analgesia have been reported as being four to six hours for tramadol alone and 12–16 hr for the tramadol-droperidol combination, where the number of daily doses were six to eight for the tramadol alone and one to two for the tramadol-droperidol combination.[2,9,16] It has been suggested that the combination of clonidine with an opioid extends the duration of analgesia by two to three times.[1,4,10,15,21] Murthy *et al.*[22] have found a lower volume of distribution for epidural tramadol and stated that the half-life was shorter than with *iv* usage. In the present study, we observed that the addition of clonidine or droperidol to tramadol extends the duration of analgesia by three times on average and, consequently, reduces daily tramadol requirements.

Studies using tramadol and tramadol-droperidol combinations found no significant sedation,[2,3,9,16,18] while all studies using clonidine have reported a prominent increase in sedation.[1,4,10,15,19] This leads us to believe that the significant increase in sedation observed in the tramadol-clonidine group was due to the addition of clonidine.

Although the studies using epidural clonidine have reported bradycardia and hypotension as the most frequent adverse effects,[1,4,10,15,19] no significant hemody-

namic adverse effects have been reported with tramadol alone or with the tramadol-droperidol combination.[1–3,12,16,18] We observed a decrease in blood pressure and heart rate from the tenth minute onwards only in the tramadol-clonidine group. This decrease did not require any intervention and no such adverse effect was detected in the other groups.

Low plasma concentrations of tramadol are observed after epidural injection, and these are insufficient to produce an analgesic effect.[2] Therefore, despite the lack of a parenteral control group, we believe that the analgesic effect of tramadol was mediated epidurally.

The most frequent side effect of epidural tramadol is nausea. The addition of droperidol to epidural opioids has a strong antiemetic effect.[1,4,15,23] In the present study, nausea was the most frequent adverse effect in the tramadol and tramadol-clonidine groups and, since no significant difference was detected between the two groups, we conclude that nausea is probably secondary to tramadol. The absence of nausea in the tramadol-droperidol group is consistent with previous studies and might be related to the antiemetic effect of droperidol.

The main adverse effects of long-term epidural droperidol are sedation, anxiety, panic, suicide and extrapyramidal side effects.[1] When used per oral, *iv* or epidural, droperidol has shown adverse effects such as QT prolongation and/or arrhythmia.[24–26] The absence of adverse effects in the present study may be secondary to the brief duration of exposure, the low doses used and the small number of patients studied.

The safety of epidural and intrathecal clonidine has been established in several studies.[1,10] No local or systemic toxic effects of epidural droperidol have been reported except for excessive sedation.[1,8,12] Finally, no systemic or local neurotoxicity has been reported with the epidural injection of tramadol.[1–3,6]

In conclusion, our results suggest that the addition of droperidol or clonidine to epidural tramadol provides a shorter onset time and a longer duration of analgesia. Droperidol seems to be a more suitable adjunct when its adverse effects and antiemetic properties are taken into consideration.

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