Comparison of tramadol and tramadol/droperidol mixture for patient-controlled analgesia

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Purpose: To compare the analgesic efficacy and side effects of tramadol vs tramadol and droperidol for post-operative patient-controlled analgesia (PCA).

Methods: Randomised, double-blind study. Thirty-four patients undergoing elective colorectal or head and neck surgery were allocated to Group 1 ($n = 18$, PCA bolus 10 mg tramadol) or Group 2 ($n = 16$, PCA bolus 10 mg tramadol + 0.1 mg droperidol). Anaesthesia was induced with fentanyl and thiopentone and maintained with O_2 , N_2O plus enflurane or isoflurane with iv morphine at doses decided by the attending anaesthetists. Muscle relaxation was achieved with atracurium or vecuronium. Patients were observed four-hourly for pain using an 11-point verbal rating scale (VRS). Nausea and vomiting, and sedation were assessed using four-point scales post-operatively. Vital signs, request for rescue anti-emetic and analgesic, and overall satisfaction were recorded.

Results: The mean nausea scores were lower in Group 2 (1.00 ± 1.33 vs 0.06 ± 0.25 at 0–8 hr, 1.22 ± 1.93 vs 0.06 ± 0.25 at 8–16 hr, $P < 0.01$; 0.81 ± 1.68 vs 0 at 32–40 hr, $P < 0.05$; Group 1 vs Group 2). The vomiting scores were also lower (0.50 ± 1.04 vs 0 at 0–8 hr, 0.67 ± 1.50 vs 0 at 8–16 hr, $P < 0.05$; Group 1 vs Group 2). Seven (39%) patients in Group 1, but none in Group 2 requested rescue anti-emetic ($P < 0.01$). There were no differences in VRS, sedation score, overall satisfaction or vital signs.

Conclusion: Tramadol and droperidol combination is superior to tramadol alone for post-operative PCA. It provides a similar quality of analgesia with less nausea and vomiting and without an increase in sedation.

Objectif : Comparer le tramadol seul avec l'association tramadol-dropéridol sous l'aspect de l'efficacité et des effets secondaires lorsque administrés pour l'analésie postopératoire autocontrôlée (PCA).

Méthodes : Étude aléatoire en double aveugle. Trente-quatre patients soumis à une chirurgie élective colorectale ou céphalo-cervicale ont été assignés au groupe 1 ($n=18$, PCA avec tramadol 10 mg en bolus) ou au groupe 2 ($n=16$, PCA avec tramadol 10 mg+ dropéridol 0,1 mg en bolus). L'anesthésie induite au fentanyl et au thiopentone était maintenue avec O_2/N_2O et enflurane ou isoflurane et morphine iv aux doses décidées par l'anesthésiste en charge. La curarisation était réalisée avec de l'atracurium ou du vécuronium. Après l'intervention, la douleur a été cotée aux quatre heures sur une échelle verbale simple (EVS) en onze points. Les nausées les vomissements et la sédation ont été estimés sur une échelle de quatre points. Les signes vitaux, les demandes d'antiémétiques et d'analésiques, et le degré général de satisfaction étaient notés.

Résultats : Les scores moyens de nausée étaient inférieurs dans le groupe 2 ($1,00 \pm 1,33$ vs $0,06 \pm 0,25$ à 0–8 h ; $1,22 \pm 1,93$ vs $0,06 \pm 0,25$ à 8–16 h, $P < 0,01$; $0,81 \pm 1,68$ vs 0 à 32–40 h, $P < 0,05$; groupe 1 vs groupe 2). Les scores de vomissement étaient aussi inférieurs ($0,50 \pm 1,04$ vs 0 à 0–8 h, $0,67 \pm 1,50$ vs 0 à 8–16 h, $P < 0,05$, groupe 1 vs groupe 2). Sept patients (39%) du groupe 1, mais aucun du groupe 2, ont demandé un antiémétique de sauvetage ($P < 0,01$). L'EVS, le score de sédation, le degré de satisfaction et les signes vitaux ne différaient pas.

Conclusion : Pour l'analésie postopératoire en PCA, l'association tramadol-dropéridol est supérieure au tramadol seul. Elle procure une analésie d'aussi bonne qualité, provoque moins de nausées et de vomissements et n'augmente pas la sédation.

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MIXING droperidol with opioids in patient-controlled analgesia (PCA) reduces the incidence of nausea and vomiting in the post-operative period.^{1,2} However, a mixture of droperidol and morphine in PCA causes excessive sedation in the first 12 hr after surgery.² The sedative effect associated with the use of droperidol as an anti-emetic in PCA might be minimised by using a less sedating opioid. Tramadol is an effective opioid analgesic which produces less sedation than morphine.³ Therefore, we designed this study to compare, in a randomised, double-blind manner, the efficacy and side effect profiles of tramadol and a mixture of tramadol and droperidol for postoperative PCA.

Methods

The study was approved by the institutional Ethics Committee. Inclusion criteria were patients who would undergo elective colorectal or head and neck surgery. As differences in age or sex of the patient population might be associated with differences in the risk of nausea, vomiting or sedation post-operatively, we included patients undergoing these two types of procedures who had similar demographic characteristics. Moreover, the procedures themselves were not recognised as risk factors for post-operative nausea, vomiting or sedation. Exclusion criteria were: (1) < 18 yr old, (2) ASA class $\geq$ IV, (3) mentally incapable of using PCA, (4) allergy to tramadol or droperidol, (5) history of substance or alcohol abuse, (6) pregnant or lactating women and (7) refusal to participate in study.

All eligible patients, after giving informed written consent to participate in the study, were allocated randomly to one of two treatment groups determined by opening identical opaque sealed envelopes which contained the instructions on preparing the required solution for PCA. The envelopes were prepared by an assistant uninvolved in the study, then shuffled and mixed in a box. The attending anaesthetist would pick randomly from the box before preparing the solution for PCA. Both the patients and the nurses responsible for the post-operative care and observation were blinded to the grouping of the patients.

Group 1 patients had 10 mg·ml⁻¹ tramadol in normal saline and Group 2 patients 10 mg·ml⁻¹ tramadol plus 0.1 mg·ml⁻¹ droperidol in normal saline in their pumps. All pumps were set to an identical setting with PCA bolus of 1 ml (corresponding to 10 mg tramadol in Group 1 and 10 mg tramadol plus 0.1 mg droperidol in Group 2). The PCA pump was prepared by the attending anaesthetist according to the results of randomisation during the intraoperative period. The syringes were labelled as 'study opioid.' No basal infusion was prescribed. The lockout interval was set to

five minutes. The one hour maximum dose was 0.1–0.15 ml·kg⁻¹ body weight. All patients received their drug via a Graseby™ 3300 PCA pump through a dedicated intravenous line. In both groups, 10 mg metoclopramide *iv* and 0.4 mg·kg⁻¹ meperidine *im* were prescribed every four hours on request as the rescue anti-emetic and analgesic respectively. A loading dose of droperidol was not used because the concomitant use of a loading dose of droperidol and its addition to a PCA morphine solution has been shown to increase sedation while having no additional benefit on the prevention of nausea and vomiting.⁴

During the pre-operative assessment, all patients were instructed on the use of PCA and no premedication was prescribed. Anaesthesia was induced with 50–100 µg fentanyl followed by 4–5 mg·kg⁻¹ thiopentone, and muscle relaxation was provided with a loading dose of 0.5–0.6 mg·kg⁻¹ atracurium or 0.1 mg·kg⁻¹ vecuronium. The tracheas were then intubated and intermittent positive pressure ventilation was started. Anaesthesia was maintained with a mixture of O₂, N₂O with enflurane or isoflurane, supplemented with intermittent boluses or infusion of atracurium or vecuronium. Irrespective of the grouping, all patients received incremental doses of morphine *iv* for intraoperative analgesia. The dose was decided by the attending anaesthetist. Intraoperative use of tramadol was avoided due to the concern over the increased risk of awareness.⁵ At the end of the procedure, the tracheas were extubated and the patients sent to recovery room. The PCA was started in the recovery room with the study drug.

When analgesia was required in the recovery room, patients activated the PCA pumps themselves after receiving further instruction from the recovery room nurses. The nurses delivered the initial boluses if the patients were too drowsy to press the PCA button. Monitoring included blood pressure (BP), pulse (P), continuous oxygen saturation (SpO₂) and respiratory rate (RR). Arterial blood gas was performed if RR < 10 or if clinically indicated. Analgesia was assessed by a verbal rating scale (VRS)⁶ from 0 to 10 (0 = no pain, 10 = the worst pain imagined). The VRS was measured both at rest and during coughing or movement, hourly in the first 24 hr after operation, and four-hourly thereafter. Both nausea and vomiting were assessed on a four point scale: 0 = no nausea/vomit, 1 = mild nausea/vomit, patient not requesting metoclopramide, 2 = nausea/vomit, patient requesting metoclopramide and 3 = nausea/vomit resistant to metoclopramide. Sedation was also assessed on a four point scale: 0 = fully awake, 1 = slightly drowsy, 2 = sleeping but easily arousable and 3 = unconscious, unrousable. All observations were recorded every four hours. In addition, the number of

demands made on the pump, and the total dose of drug consumed were recorded daily. Use of rescue analgesic or anti-emetic and any other discomfort were recorded daily. An overall assessment of the analgesic technique as good, fair or unsatisfactory was given by the patients on discontinuation of the PCA pump. Major complications such as a sedation score of 3, respiratory depression with $SpO_2 < 90\%$ for > 10 min with optimal O_2 therapy by mask or $RR < 8$ bpm and $PaCO_2 > 50$ mmHg, or requiring tracheal re-intubation and ventilatory support were recorded. The patients were followed up every day by an anaesthetist of the Pain Management Team who was not blinded to the grouping of the patients. However, the Pain Management Team was only responsible for the clinical well-being of the patient, but would not enter any data regarding pain score or other side effects into the patients files. Should the patients clinical condition necessitate any change in the analgesic technique or setting of the PCA pump, the patient was excluded from the study. This ensured safety of the patients as well as blindness in the data collected for analysis.

The PCA pumps were kept for at least 48 hr unless the patient requested earlier discontinuation. The reason for discontinuation was recorded. Refilling of the syringes was done by one of the investigators to keep the nurses on the wards blinded. If patients required the PCA pump after 48 hr, they were continued but no further data were collected.

We aimed to achieve an incidence of nausea of about 10% in our patients receiving droperidol. Assuming an incidence of nausea of around 60% in patients receiving PCA with systemic opioids,^{1,2} power analysis with an α error level at 0.05 and a statistical power of 80% to detect this difference indicated at least 17 patients were required in each group. The true incidence of nausea in patients receiving PCA tramadol was unavailable in the literature. This sample size would also detect an inter-group difference in sedation score of 1, assuming a standard deviation of 1 at the same α error level with the same power.

Statistical analysis was performed using the software programme Statistica release 4.5 (StatSoft™, Tulsa™, Oklahoma, USA). Nonparametric data such as nausea and vomiting scores, pain score and patient demographic variables were analysed by Mann-Whitney *U* test and Chi-squared test as appropriate. Parametric data were compared by two tailed independent *t* tests.

Results

A total of 34 patients undergoing colorectal or head and neck surgery procedures were studied; 18 in Group 1 and 16 in Group 2. There were no differences in the age, sex or body weight of the patients in the two groups. There was only a minor difference in the ASA status. The operation duration, the amount

of blood loss and the dose of intraoperative morphine administered were also not different. The types of operation performed were also similar (Table I).

No differences were observed in the four-hourly pain scores both at rest and during cough or movement in the two treatment groups throughout the study (Figure 1). In the initial 24 hr, pain scores were recorded hourly and the mean pain score of any four hour period were taken and presented. The number of demands made by patients on the PCA pump, the ratio of total demands to 'good demands' (tries/good ratio), the total dose of drug con-

TABLE I Demographic data and operative details

Group	1	2	P
	(n=18)	(n=16)	
Age	61.8 $\pm$ 8.7	57.9 $\pm$ 14.6	ns
Sex (M/F)	9/9	8/8	ns
Body weight (kg)	56.5 $\pm$ 10.6	54.6 $\pm$ 8.3	ns
ASA * I	4 (22%)	9 (56%)	<0.05
II	11 (61%)	6 (38%)	
III	3 (17%)	1 (6%)	
Procedure: colorectal	14 (78%)	12 (75%)	ns
head & neck	4 (22%)	4 (25%)	
Operation duration (min)	221.9 $\pm$ 144.3	214.7 $\pm$ 126.4	ns
Blood loss (ml)	550.0 $\pm$ 409.5	386.7 $\pm$ 311.4	ns
Intraop morphine (mg)	8.1 $\pm$ 3.2	7.8 $\pm$ 2.9	ns

Mean $\pm$ SD

*Number (%)

All analysis Students *t* test except ASA by Mann-Whitney *U*-test and sex by Chi-squared test

FIGURE 1 Verbal Rating Scale (VRS) pain scores, at rest and during coughing. Mean $\pm$ SD. There were no between group differences throughout the study.

sumed and the number of requests for rescue analgesic during the study period were also not different (Table II).

Nausea and vomiting were compared between the two groups for each eight-hour period post-operatively. Hence, over the 48-hr of data collection, there were six pairs of comparisons for each patient. Since a nausea/vomit score was recorded every four hours, the sum of the scores in any eight-hour period was used for a particular patient. The maximum possible score in an eight-hour period was 6, and the minimum 0. Nausea scores were higher in Group 1 (Figure 2) in three eight-hour periods, namely 0–8 hr ($P < 0.01$), 8–16 hr ($P < 0.01$) and 32–40 hr ($P < 0.05$). Vomit scores were

TABLE II Analgesic requirement during the study period

Group	1	2	P
	(n=18)	(n=16)	
Number of demands			
0–24hr	146.9 ± 243.5	150.9 ± 191.1	ns
24–48hr	54.4 ± 90.2	74.9 ± 108.4	ns
Tries/good ratio			
0–24hr	3.2 ± 2.2	4.2 ± 6.1	ns
	1.9 ± 1.2	2.9 ± 2.5	ns
Total dose PCA (mg)	650.0 ± 570.5	592.5 ± 431.0	ns
Request rescue analgesic*			
none	16 (88%)	16 (100%)	ns
once	1 (6%)	0	
twice	1 (6%)	0	

Mean ± SD

*Number (%)

Number of demands and request for rescue analgesic analysed by Mann-Whitney *U*-test

Tries/good ratio and total dose analysed by Students *t* test

FIGURE 2 Eight-hourly nausea scores. Mean ± SD. Nausea scores were lower in Group 2 at 0–8 and 8–16 hr ($P < 0.01$) and at 32–40 hr ($P < 0.05$)

also higher in Group 1 (Figure 3) in two eight-hour periods, namely 0–8 hr ($P < 0.05$) and 8–16 hr ($P < 0.05$). No patient in Group 2 vomited. Seven patients in Group 1 requested metoclopramide during the study period, while no patient in Group 2 made this request ($P < 0.01$).

There were no differences in sedation scores between the two groups at each eight-hour periods (Figure 4). There were no differences in the vital signs recorded every four hours.

FIGURE 3 Eight-hourly vomit scores. Mean ± SD. Vomits scores were lower in Group 2 at 0–8 and 8–16 hr ($P < 0.05$)

FIGURE 4 Eight-hourly sedation scores. Values are mean ± SD. There were no between group differences throughout the study.

In Group 1, 16 (88.9%) patients rated their overall PCA experience good, one (5.6%) rated fair and one (5.6%) rated bad. In Group 2, 12 (75.0%) rated good, four (25.0%) rated fair and none rated bad. The differences were not statistically significant. No major complication occurred in any of the study patients.

Discussion

Our study showed a reduced incidence and severity of nausea and vomiting in patients receiving a mixture of tramadol and droperidol for PCA compared with those receiving tramadol alone. There was no increase in sedation when tramadol was mixed with droperidol.

The use of PCA opioids is an effective and safe analgesic technique for postoperative pain control. The most frequent complication associated with the technique is nausea and vomiting. This complication has been reported by patients⁷ to be even worse, at times, than pain and contributes to a less than optimal quality of analgesia by inhibiting patients from making the number of demands they would otherwise do. Various solutions have been proposed, concentrating mainly on its prevention. The more promising are the use of a mixture of morphine and droperidol,^{1,2} or of 5HT₃ antagonists.^{8,9} However, the former has been associated with an increased incidence of sedation,² whereas 5HT₃ antagonists are too expensive¹⁰ to be used for routine prophylaxis.

Tramadol is an opioid analgesic acting as an agonist at μ -receptors, and by inhibition of reuptake of 5HT and noradrenaline in the central nervous system. Its major difference from 'conventional opioids,' such as morphine and meperidine, is in its side effect profile. It has less sedative effect,³ less respiratory depression,^{3,11} and less abusive potential.^{12,13} Due to these differences, tramadol is not a controlled drug in many countries where its clinical use is approved. Despite these differences, its analgesic efficacy is comparable with that of other potent opioids such as morphine administered intravenously,³ or epidurally.¹⁴ However, its potential to cause nausea and vomiting, when used for post-operative analgesia, is not different from the 'conventional' opioids.^{3,11} Theoretically, the relative lack of sedation should make a mixture of tramadol and droperidol less sedative than a morphine and droperidol mixture, and yet achieve a lower incidence of nausea and vomiting than when the drug is used alone. This has been demonstrated in our study.

A mixture of tramadol and droperidol is superior to tramadol alone for postoperative PCA. It combines good analgesia with reduced nausea and vomiting. This mixture of tramadol and droperidol may also be useful in the setting of ambulatory surgery or ambulatory PCA for chronic pain patients to provide long

lasting analgesia, without excessive sedation and nausea and vomiting. However, there is still room for improvement. We found an overall incidence of nausea of about 20% in our patients in the tramadol and droperidol mixture group. It would be interesting to see whether the use of 5HT₃ antagonists, as suggested by Vickers,¹⁴ would reduce this further. However, an adverse effect of 5HT₃ antagonists on the analgesic efficacy of tramadol is theoretically possible. Although the negative influence of 5HT₃ antagonists on analgesic efficacy has been shown to be insignificant with 'conventional' opioids,¹⁵ this may be different with tramadol as inhibition of 5HT uptake also contributes to the analgesic effect of this drug.

There are several limitations to our study. First, the patients were not at highest risk for post-operative nausea and vomiting. Whether the tramadol and droperidol mixture will be as promising in gynaecological patients, for example, is unknown. Second, despite the difference in incidence and severity of nausea and vomiting, we were unable to demonstrate either increased tramadol consumption or superior patient satisfaction in the tramadol/droperidol group. This probably reflects the fact that patient satisfaction when receiving an analgesic technique depends on many factors. The successful control of nausea and vomiting by rescue metoclopramide in some patients, and the relatively small size of our study may also contribute to this.

In conclusion, our study demonstrated that a mixture of tramadol and droperidol is associated with a reduced incidence and severity of nausea and vomiting compared with tramadol alone when used in PCA after colorectal or head and neck surgery procedures. This was not associated with any differences in the degree of sedation or quality of analgesia.

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