The use of tramadol and morphine for pain relief after abdominal hysterectomy

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Summary

Objective: The aim of this study was to determine whether the addition of a tramadol infusion to morphine patient-controlled analgesia (PCA) results in improved analgesic efficacy compared with morphine PCA alone after abdominal hysterectomy.

Methods: Sixty patients undergoing abdominal hysterectomy were randomized into two groups, each receiving IV morphine PCA after surgery. The tramadol group received a loading dose of tramadol (1 mg/kg) at skin closure and a postoperative infusion of tramadol at 0.2 mg/kg/h. The control group received an equivalent volume of saline at skin closure and a postoperative saline infusion.

Results: The addition of a tramadol infusion to morphine PCA was associated with lower pain scores, a reduction in PCA morphine requirements (27 ± 4.6 mg vs 40.5 ± 5.4 mg over 24 h) and improved patient satisfaction with pain relief ($p < 0.05$). No intergroup differences were found with regard to sedation, nausea and antiemetic use ($p > 0.05$).

Conclusion: The addition of a tramadol infusion to morphine PCA resulted in improved analgesic efficacy and reduced morphine requirements compared with morphine PCA alone after abdominal hysterectomy.

Key words: Tramadol; Morphine; Patient-controlled analgesia; Abdominal hysterectomy.

Introduction

Tramadol is a centrally-acting analgesic drug, effective in the treatment of moderate to moderately severe pain with a relatively low potential for respiratory depression and addiction [1]. Tramadol has a low affinity for m-opioid receptors and its antinociceptive action in some experimental models is only partially antagonized by naloxone [1]. Therefore, tramadol seems to have a non-opioid mechanism of action contributing to its analgesic potency. The analgesic efficacy of tramadol is also reduced by α 2 adrenoceptor blockade and its antinociceptive effect is likely to be mediated mainly by inhibition of the reuptake of norepinephrine and serotonin in the central nervous system [2].

The analgesic efficacy of tramadol has been reported to be similar to that of morphine or alfentanil and superior to that of pentazocine [3]. The efficacy of tramadol for the management of moderate to severe postoperative pain has been demonstrated in several surgical populations [4-6]. In patients undergoing abdominal hysterectomy, intraoperative administration of tramadol was reported to be as effective as morphine for postoperative analgesia [7]. Although there are a number of clinical trials comparing the postoperative analgesic efficacy of morphine to tramadol [4, 5-7] there is much less information about the addition of tramadol to morphine. The clinical benefit in using tramadol as an adjunctive drug to morphine after abdominal surgery was reported in a previous study [8]. There is a possibility that concomitant use of tramadol and morphine may provide an additive or synergistic effect through nonopioid mechanisms of action acting in synergy with opioid effects. The aim of this study was to determine whether the addition of a tramadol infusion to morphine patient-controlled analgesia (PCA) results in improved analgesic efficacy compared with morphine PCA alone after abdominal hysterectomy.

Materials and Methods

Sixty ASA physical status I or II patients, between the ages of 18 and 65 years, scheduled for elective abdominal hysterectomy were included in this double-blinded and randomized controlled study. The study was approved by our institutional ethics committee and all patients gave written informed consent. Preoperatively, patients were instructed on the use of the patient-controlled analgesia (PCA) device and the visual analog scale (VAS) for pain assessment. Exclusion criteria included inability to use the PCA device, history of chronic pain, long-term use of opioid medications, psychiatric disorders involving the use of antidepressants – especially monoamine oxidase inhibitor or selective serotonin reuptake inhibitor drugs, known history of motion-sickness, epilepsy, substance or alcohol abuse, allergy to opiates or tramadol and hepatic or renal impairment.

All patients underwent abdominal hysterectomy via a lower abdominal incision performed by the same team of surgeons. Premedication and anesthetic management were standardized in both groups. Premedication comprised diazepam 10 mg orally, administered two hours before surgery. After insertion of an intravenous cannula and placement of routine intraoperative monitoring devices, such as an electrocardiograph, pulse oximetry, capnograph and noninvasive blood pressure monitor (Datex-Ohmeda, Instrumentarium Corp., Helsinki, Finland), patients were preoxygenated. Anesthesia was induced with 1 μg/kg remifentanil, 2.5 mg/kg propofol and maintained with 1-2% sevoflurane in a mixture of 65% nitrous oxide and 35% oxygen. Remifentanil infusion was maintained at 0.25-0.5 μg/kg/min. Neuromuscular relaxation was induced by 0.6 mg/kg rocuronium and maintained by 0.2 mg/kg bolus administration when needed. At the last skin-stitch, remifentanil infusion and anesthetic gases were terminated and patients were

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allocated randomly into two groups. The Tramadol group (n = 30) received a loading dose of tramadol (1 mg/kg) at skin closure and the loading dose of tramadol was diluted to a volume of 5 ml with normal saline to maintain blinding of the anesthesiologist administering the drug. The Control group (n = 30) received an equivalent volume of saline (5 ml) at skin closure. The trachea was extubated on awakening while breathing spontaneously after which patients were transported to the intensive care unit (ICU).

In the ICU, the Tramadol group (n = 30) received a postoperative infusion of tramadol at 0.2 mg/kg/h for 24 h and the tramadol infusion was prepared so that 0.2 mg/kg/h tramadol was delivered at a rate of 2 ml/h. The Control group (n = 30) received a postoperative saline infusion at a rate of 2 ml/h for 24 h. All patients were supplied with a PCA machine set to deliver IV morphine boluses in 2 mg increments (bolus dose: 2 mg, lock-out time: 15 min, 4 hour limit: 20 mg). An anesthesiologist who was blinded to the study drugs assessed postoperative pain by using a visual analog scale (VAS, 0 = no pain, 10 = worst possible pain) at the time of arrival to the ICU and at postoperative 1, 2, 3, 4, 8, 12, 16, 20 and 24 hours. Morphine consumption by PCA and vital signs (mean arterial pressure, heart rate, respiratory rate and oxygen saturation [SpO_2]) were also recorded by the blinded anesthesiologist at these time intervals. Patients assessed as being in pain, on the basis of a VAS score > 4, were offered rescue medication of morphine 2 mg IV bolus, repeated as necessary until adequate analgesia was obtained. The degree of sedation was rated on a four-point scale (0 = alert, 1 = arouse to voice, 2 = arouse with gentle tactile stimulation, 3 = arouse with vigorous tactile stimulation, 4 = no awareness) and the presence of postoperative nausea/vomiting was also registered (0 = none, 1 = mild, 2 = severe) at 1, 2, 3, 4, 8, 12, 16, 20 and 24 hours after arrival at the ICU. Nausea and vomiting were treated with metoclopramide 10 mg IV, followed by ondansetron if the problem persisted. Overall patient satisfaction with pain relief (excellent, good, satisfactory, poor, very poor) was assessed at 24 h after surgery. Other analgesic or sedative drugs than those mentioned above were prohibited. Patients were planned to be excluded from the study in case of inadequate analgesia (VAS ≥ 4) necessitating other treatments, such as nonsteroidal anti-inflamatory drugs. Any side-effects other than those mentioned above were recorded. The chi-square, t-test, Mann-Whitney, Fisher exact and Friedman tests were used for statistical analysis; $p < 0.05$ was accepted as significant.

Results

The patient groups were comparable ($p > 0.05$) with respect to age, weight, ASA physical status and duration of surgery (Table 1).

In the Tramadol group, there was a significant reduction in PCA morphine requirements at postoperative 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours ($p < 0.05$) when compared with the Control group (Table 2). Pain scores decreased comparably in both study groups during the postoperative study period and VAS scores were lower in the Tramadol group than in the Control group ($p < 0.05$) at all assessment times (Table 3). The overall patient satisfaction with pain relief was significantly improved in the Tramadol group ($p < 0.05$) when compared with the Control group (Table 4). There was a significant difference between groups in the mean doses of rescue morphine required during the postoperative period; patients in the Tramadol group required 3.2 ± 1.7 mg, while patients in the Control group required 5.0 ± 2.7 mg ($p < 0.05$).

Table 1. — *Patient characteristics.*

	Tramadol group (n = 30)	Control group (n = 30)
Age (Yr)	47.33 ± 5.63	48.63 ± 7.37
Weight (Kg)	68.03 ± 9.66	67.53 ± 8.16
ASA (I/II)[a]	13 / 17	14 / 16
Duration of surgery (min)	108.13 ± 27.70	99.03 ± 25.87

Data are presented as mean ± SD or [a]number of patients.

Table 2. — *Postoperative PCA morphine consumption.*

	Tramadol group (n = 30)	Control group (n = 30)
Postop 1 h	5.53 ± 2.08*	6.86 ± 2.08
Postop 2 h	8.20 ± 3.64*	11.13 ± 3.04
Postop 3 h	12.46 ± 4.65*	15.60 ± 3.76
Postop 4 h	14.80 ± 5.29*	17.93 ± 3.80
Postop 8 h	18.60 ± 6.17*	24.9 ± 6.0
Postop 12 h	20.60 ± 5.66*	29.73 ± 5.0
Postop 16 h	22.63 ± 5.62*	33.8 ± 4.55
Postop 20 h	25.26 ± 5.18*	36.86 ± 4.41
Postop 24 h	27.0 ± 4.69*	40.53 ± 5.45

Data are presented as mean ± SD.
** $p < 0.05$; between groups.*

Table 3. — *Postoperative VAS scores.*

	Tramadol group (n = 30)	Control group (n = 30)
Postop 0 h	2.9 ± 0.66*	3.83 ± 0.79
Postop 1 h	2.36± 0.76*	3.23 ± 0.43
Postop 2 h	2.26 ± 0.58*	2.70 ± 0.59
Postop 3 h	1.90± 0.60*	2.73 ± 0.52
Postop 4 h	1.60± 0.62*	2.40 ± 0.49
Postop 8 h	1.33± 0.60*	2.10 ± 0.30
Postop 12 h	1.30± 0.70*	2.16 ± 0.37
Postop 16 h	1.10± 0.66*	1.96 ± 0.41
Postop 20 h	0.66± 0.66*	1.40 ± 0.49
Postop 24 h	0.26± 0.44*	1.26 ± 0.63

Data are presented as mean ± SD.
** $p < 0.05$; between groups.*

Table 4. — *Postoperative patient data.*

	Tramadol group (n = 30)	Control group (n = 30)
Sedation score	0 (0-3)	0 (0-3)
Nausea score	0 (0-2)	0 (0-2)
Antiemetic doses[a]	0.63 ± 0.61	0.56 ± 0.56
Patient satisfaction with pain relief[b] (Exc./Good/Sat./ Poor/V. poor)	17/1/2/0/0*	0/14/16/0/0

Data are presented as median (range), [a]mean ± SD or [b]number of patients.
** $p < 0.05$; between groups.*
Exc. - excellent; Sat. - satisfactory; V. poor - very poor.

Sedation scores, nausea scores and antiemetic doses were similar ($p > 0.05$) in both groups (Table 4). All patients were hemodynamically stable and no significant intergroup differences ($p > 0.05$) were seen in hemodynamic and respiratory data (Table 5).

Table 5. — *Postoperative vital signs.*

	Tramadol group (n = 30)	Control group (n = 30)
HR (beat/min)	81.40 ± 4.35	82.76 ± 3.63
MAP (mmHg)	90.43 ± 5.25	89.76 ± 5.55
RR (bpm)	18.20 ± 1.76	18.13 ± 1.73
SpO_2 (%)	99.17 ± 1.40	99.14 ± 1.18

Data are presented as mean ± SD.
HR - heart rate; MAP - mean arterial pressure; RR - respiratory rate.

Discussion

In this study patient-controlled analgesia with morphine, alone or combined with tramadol, was well accepted by the patients. The intraoperative tramadol initial loading dose of 1 mg/kg and a postoperative infusion rate of 0.2 mg/kg/h were used in accordance with the product information sheet, which recommends a maximal daily dose of 400 mg. The addition of a tramadol infusion (0.2 mg/kg/h) following a bolus dose of 1 mg/kg proved to be a useful adjunct to morphine PCA in patients recovering from abdominal hysterectomy. The patients in the Tramadol group had lower pain scores, less PCA morphine consumption and required less rescue morphine over 24 h when compared with the patients in the Control group. The overall satisfaction with pain relief was also improved in postoperative patients given tramadol and morphine when compared to patients given only morphine. The lower pain scores, reduction in PCA morphine requirements and improved patient satisfaction in the Tramadol group indicate an improvement in analgesic efficacy when compared with the Control group. The improvement in analgesic efficacy in patients given both tramadol and morphine suggest that monoaminergic mechanisms of action of tramadol are acting in synergy with opioid effects. The monoaminergic actions of tramadol were shown in an experimental model where tramadol blocked noradrenaline uptake in cortical synaptosomes and brain slices [8]. Tramadol was also shown to block 5-hydroxytryptamine uptake in frontocortical synaptosomes [9]. These experimental data and the fact that α 2 adrenoceptor blockade reduces its analgesic efficacy suggest that block of monoamine uptake contributes to tramadol's analgesic efficacy. Recent investigations in healthy volunteers also confirm the hypothesis that the monoaminergic system is involved in the mechanism of action of tramadol [2].

In several surgical populations, tramadol was shown to be as effective and safe as morphine for the treatment of postoperative pain [4-6, 10, 11]. Maximum analgesia occurs 45 min after IV administration, therefore tramadol should preferably be given during the final stages of a surgical procedure [10]. Coetzee et al compared the immediate postoperative effects of tramadol or morphine administered during wound closure in patients undergoing abdominal hysterectomy [11]. They showed that three mg/kg tramadol was as effective as 0.2 mg/kg morphine for controlling pain in the immediate postoperative period. Furthermore, they found a more rapid recovery of psychomotor function with tramadol, probably caused by the lack of significant sedating effects [11]. In fact, the potential advantages of administering tramadol for postoperative pain relief include its limited sedating and respiratory depressant effects [11-14]. In this study, the loading dose of tramadol was given at skin closure to ensure that it provides analgesia during the early postoperative period. The addition of a tramadol infusion to morphine PCA provided effective postoperative analgesia without any adverse respiratory or cardiovascular events. In some previous studies, the administration of tramadol via bolus doses for pain relief during the postoperative period resulted in an increased incidence of nausea and vomiting [3, 15-17]. The continuous infusion rate of tramadol (0.2 mg/kg/h) used in this study was well tolerated and patients had a small incidence of nausea. The mean antiemetic doses required were also similar in both study groups.

A previous study investigated the use of the combination of morphine and tramadol for postoperative analgesia in patients undergoing upper and lower abdominal surgery [8]. The anesthetic technique including intraoperative opiate administration was at the discretion of the anesthesiologist and patients received either intraoperative morphine, fentanyl or meperidine. The technique of combining morphine and tramadol for postoperative analgesia provided a reduction in morphine requirements and an increase in subjective analgesic efficacy, but there was no improvement in pain scores [8]. In this study we included a more homogeneous group of patients (all female) undergoing abdominal hysterectomy with a lower abdominal incision. Anesthetic management was standardized and all patients received an intraoperative remifentanil infusion. The ultra-short-acting opioid remifentanil was chosen because it has a context-sensitive half-life of three minutes and leaves no residual opioid effects after termination of its infusion. There were significant differences between tramadol and control groups with regard to pain scores, morphine consumption and patient satisfaction with pain relief.

Conclusion

Although the combination of a tramadol infusion with morphine PCA is a complex analgesic regimen increasing the work-load of nursing personnel, we have demonstrated clinical benefit in using this technique. The addition of a tramadol infusion to morphine PCA resulted in increased analgesic efficacy and reduced morphine requirements compared with morphine PCA alone after abdominal hysterectomy.

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