The efficacy of intravenous versus epidural tramadol with patient-controlled analgesia (PCA) in gynecologic cancer pain

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Summary

We attempted to compare the analgesic effects of tramadol infusion intravenously and epidurally administered through a patient-controlled analgesia (PCA) method for postoperative analgesia following gynaecological cancer surgery.

Forty patients undergoing elective cancer surgery, included in the American Society of Anesthesiologists (ASA) class II and III, were randomly placed into two groups. The patients in the intravenous (IVA) group were administered a 20 mg bolus of tramadol intravenously and the patients in the epideral analgesia (EA) group epidurally five minutes before induction. The PCA equipment was programmed to deliver 20 mg of tramadol as a bolus dose, with a lock-out time of 15 minutes, at a 10 mg/hour infusion rate in both groups.

A visual analogue scale (VAS) and patient satisfaction as well as haemodynamic and respiratory parameters were determined at given times postoperatively. Total tramadol consumption at 24 hours and side-effects were recorded.

There was no difference between groups based on haemodynamic and respiratory parameters whereas there was a significant difference based on tramadol consumption, VAS and side-effects of tramadol and patient satisfaction between groups. VAS values of patients, 6.85 ± 1.34 and 3.00 ± 1.58, respectively, for the IVA group (group 1) and the EA group (group 2) were found to be significantly different. Postoperative patient satisfaction was higher was in group 2 than in group 1 (3.45 and 2.7, respectively).

In conclusion, epidural administration of tramadol through the PCA method following gynecologic cancer surgery was found to be a more effective analgesia in lower doses when compared to the intravenous administration.

Key words: Postoperative analgesia; Patient-controlled analgesia; Tramadol; Epidural; Intravenous.

Introduction

Postoperative pain relief can be achieved by several methods, including the use of systemic opioid and regional anesthesia with intrathecally or epidural opioid or local anaesthesia. On-demand analgesia using a patient-controlled analgesia (PCA) system is regarded as the ideal option for systemic opioid analgesia. Tramadol has now been used extensively and evaluated over the past 20 years. Tramadol may interact with μ-opioid receptors weakly compared to morphine [1]. Due to less respiratory depression tramadol has become very popular for the management of postoperative pain [2, 3]. It is also effective for postoperative pain relief by the oral, rectal, intravenous or intramuscular routes as well as epidurally [4-6].

The aim of this study was to evaluate the efficacy of intravenous patient-controlled analgesia versus epidural tramadol infusion in the treatment of postoperative gynaecologic pain.

Materials and Methods

The study was approved by the Suleyman Demirel University Ethics Committee. Forty patients (aged 35-78 years, ASA class II or III), undergoing major elective gynaecologic cancer surgery (ovarian, cervical, endometrial cancer), gave written informed consent. Patients who had drug dependence, alcoholism, or psychiatric diseases were excluded from the study. The evening before surgery the patients were instructed on the use of the PCA equipment (Abbott, Lifecare Infuser). All patients were premedicated with 5 mg midazolam and 0.5 mg atropine intramuscularly after eight hours of fasting.

Patients in group 2 were placed in a lateral position (L_{3-4} or L_{4-5}) and the intervertebral space was punctured by using a loss of resistance method with an 18-gauge Tuohy needle 20 min before surgery. After the test dose of 3 ml lidocaine injection the catheter was replaced. General anaesthesia was induced using 5 mg/kg, thiopentone and 0.1 mg/kg vecuronium with 1 μg/kg fentanyl. Anaesthesia was maintained with 50% N_2O/O_2 50%, sevoflurane 2-3% and 0.01 mg/kg vecuronium. The neuromuscular blockade was antagonized after the operation using 1 mg neostigmine and 0.5 mg atropine. All patients received prophylactic antiemetic at a dose of 10 mg metoclopramide.

Patients were randomly divided into two groups. Group 1 (n = 20) received intravenous infusion; group 2 (n = 20) received epidural tramadol infusion after a 20 mg bolus 5 min prior to anaesthesia induction. The PCA equipment was programmed to deliver 20 mg of tramadol as a bolus dose and the maximum 4-hour dose was 200 mg with the lock-out time being 15 minutes at a 10 mg/hour infusion rate in both groups.

After the patients were fully oriented and the procedure had been explained again, they left the recovery room and were placed in routine wards. All patients were continuously supervised and evaluated by the same physician who did not know the groups over the 24-hour period.

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Subjective pain was assessed by the patient using a 10 cm visual analogue scale (VAS; no pain = 0, severe pain = 10). Patient satisfaction was assessed using a scale of 1-4 (1 = no satisfaction, 2 = mild satisfaction, 3 = moderate satisfaction, 4 = full satisfaction). Patient subjective satisfaction with pain management was assessed with the question: "Are you satisfied with the pain relief?" in order to meet that scale.

When the patient's subjective pain still exceeded 3, a 50 mg bolus of tramadol was given intravenously in group 1 and 20 mg was given epidurally in group 2 as required to maintain analgesia.

Patient age, height and weight were recorded. Arterial pressure, heart rate, respiratory rate, peripheral oxygen saturation (pulse oxymetry), VAS and patient satisfaction were recorded at predetermined intervals (postoperatively 1, 2, 3, 4, 5, 6, 12 and 24 hours). Data recorded also included the total amount of tramadol as well as the incidence of side-effects.

For statistical analysis, the repeated measures were used according to the first hour compared to other hours within groups with the paired samples t-test, Friedman test and Kendall's W-test. Comparison between groups was performed with the independent samples t-test.

The Pearson chi-square test was used for statistical comparison of complications.

Results

Patient characteristics are presented in Table 1. The two groups were comparable in age, weight, and height ($p > 0.05$).

Tramadol infusion did not cause significant differences in arterial pressure or heart rate after surgery in either the intravenous or epidural group (Table 2).

There were no differences in time to respiratory rate changes or in oxygen saturation between groups ($p > 0.05$, Table 3). The respiratory rate decreased slightly but did not fall below 12/min in either group.

Pain scores of patients were different between groups. VAS values of patients in group 1 were 6.85 ± 1.34 and 3.00 ± 1.58 in group 2. The values between groups was found to be significantly different in the first postoperative hour ($p < 0.000$, Table 4). Moreover the difference was followed-up during the postoperative period. The values were closer only at the sixth hour ($p = 0.047$) (Figure 1).

Mean analgesic consumption was 312.34 ± 54.32 mg ± SD and 296.25 ± 33.19 mg ± SD in groups 1 and 2, respectively ($p = 0.256$, Table 5). Patient demand (8.35 ± 1.69 and 7.75 ± 1.65) and duration of PCA were found to be insignificant between groups (Table 6).

Table 1. — *Patient characteristic data.*

	Group 1 (IVA)	Group 2 (EA)	p values
Age (year ± SD)	54.20 ± 10.75	48.15 ± 10.54	0.080
Weight (kg ± SD)	63.60 ± 5.57	67.25 ± 6.02	0.053
Height (cm ± SD)	162.65 ± 4.24	165.35 ± 4.67	0.063

Table 2. — *Patient haemodynamic values and statistical signifi-cance.*

		Group 1(IVA)	p values[1]	Group 2 (EA)	p values[2]
SAP (mmHg±SD)	1 hour	139.10 ± 13.16	–	129.70 ± 7.97	–
	2 hour	134.90 ± 1071	0.137	127.05 ± 9.09	0.166
	3 hour	135.05 ± 11.91	0.157	126.05 ± 11.11	0.120
	4 hour	134.75 ± 7.39	0.103	127.05 ± 9.90	0.178
	5 hour	133.35 ± 11.06	0.071	126.30 ± 8.32	0.097
	6 hour	135.55 ± 9.94	0.171	129.05 ± 10.10	0.411
	12 hour	134.65 ± 9.95	0.118	125.70 ± 8.49	0.066
	24 hour	132.95 ± 10.02	0.052	126.60 ± 9.30	0.132
HR (beat/min±SD)	1 hour	82.30 ± 4.74	–	77.10 ± 4.66	–
	2 hour	79.50 ± 6.15	0.057	74.90 ± 5.21	0.083
	3 hour	84.50 ± 4.81	0.076	75.40 ± 4.82	0.132
	4 hour	79.95 ± 7.75	0.128	74.80 ± 5.63	0.084
	5 hour	79.50 ± 7.40	0.082	75.05 ± 3.94	0.070
	6 hour	83.65 ± 4.90	0.190	75.10 ± 4.75	0.093
	12 hour	78.80 ± 8.55	0.060	74.15 ± 6.48	0.053
	24 hour	83.80 ± 5.79	0.188	77.60 ± 7.04	0.396

[1]Significance between the first hour data and other data in group 1.
[2]Significance between the first hour data and other data in group 2.

Table 3. — *Patient oxygen saturation, respiratory rates and statistical significance.*

	Oxygen Saturation			Respiratory Rate		
	Group 1 (IVA)	Group 2 (EA)	p values	Group 1 (IVA)	Group 2 (EA)	p values
1 hour	96.75 ± 1.40	96.30 ± 1.34	0.307	13.90 ± 1.02	14.05 ± 1.05	0.649
2 hours	96.25 ± 1.37	96.50 ± 1.70	0.611	13.80 ± 0.95	13.65 ± 1.03	0.636
3 hours	96.60 ± 1.31	96.15 ± 1.18	0.261	14.25 ± 0.91	13.70 ± 0.97	0.073
4 hours	96.40 ± 1.14	96.85 ± 1.56	0.305	13.85 ± 1.03	14.10 ± 0.91	0.423
5 hours	96.45 ± 1.27	97.15 ± 1.08	0.069	13.80 ± 0.95	14.30 ± 0.73	0.070
6 hours	97.15 ± 1.03	96.55 ± 1.31	0.118	14.05 ± 0.94	13.90 ± 1.11	0.649
12 hours	96.20 ± 1.23	97.00 ± 1.48	0.07	14.20 ± 1.10	14.55 ± 0.68	0.236
24 hours	96.55 ± 1.53	96.95 ± 1.53	0.415	13.80 ± 1.00	14.20 ± 1.19	0.259
Total mean	96.54 ± 0.37	96.68 ± 0.39	0.284	13.95 ± 0.33	14.05 ± 1.32	0.342

Table 4. — *Patient VAS data (mean ± standard deviations) in groups and statistical comparisons.*

	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	12 hours	24 hours
Group 1 (IVA)	6.85 ± 1.34	6.00 ± 1.12	5.25 ± 1.11	3.85 ± 1.08	3.10 ± 1.20	1.60 ± 0.75	1.30 ± 0.57	1.15 ± 0.48
	p values[1]	< 0.000	< 0.000	< 0.000	< 0.000	< 0.000	< 0.000	< 0.000
Group 2 (EA)	3.00 ± 1.58	2.55 ± 1.09	2.10 ± 0.78	1.80 ± 1.10	1.50 ± 0.68	1.10 ± 0.78	0.80 ± 0.76	0.30 ± 0.57
	p values[2]	0.016	0.003	0.001	0.001	< 0.000	< 0.000	< 0.000
Between groups[3]	< 0.000	< 0.000	< 0.000	< 0.000	< 0.000	0.047	0.024	< 0.000

[1]Comparison between the first hour and repeated measured data in group 1; [2]Comparison between the first hour and repeated measured data in group 2; [3]Comparison between groups 1 and 2.

Table 5. — *Patient tramadol consumption excluding bolus doses and statistical significance.*

	Group 1 (IVA)	Group 2 (EA)	p values
1 hour	350.50 ± 46.95	326.00 ± 36.18	0.072
2 hours	342.75 ± 43.99	319.50 ± 35.31	0.073
3 hours	334.50 ± 45.93	312.00 ± 36.36	0.094
4 hours	322.50 ± 55.14	302.50 ± 35.67	0.181
5 hours	207.25 ± 54.08	293.50 ± 31.50	0.332
6 hours	293.00 ± 61.90	286.00 ± 33.62	0.659
12. hours	276.00 ± 70.81	275.50 ± 33.00	0.977
24. hours	271.75 ± 74.67	255.00 ± 29.82	0.357
Total mean	312.34 ± 54.32	296.25 ± 33.19	0.265

Table 6. — *Patient demands and statistical comparisons.*

	Group 1 (IVA)			Group 2 (EA)		
	Mean ± SD	Min	Max	Mean ± SD	Min	Max
Demands/ patient[1]	8.35 ± 1.69	5	11	7.75 ± 1.65	4	10
Duration of PCA (hrs)[2]	21.90 ± 1.80	18	24	20.95 ± 1.95	18	24

[1]p = 0.264; [2]p = 0.113.

Table 7. — *List of side-effects observed in both groups.*

	Group 1 (IVA)	Group 2 (EA)	p values
Nausea	2	1	0.548
Vomiting	–	–	–
Sedation	2	1	0.548
Urinary retention	1	-	0.311
Dizziness	–	–	–
Flushing (Face)	–	–	–

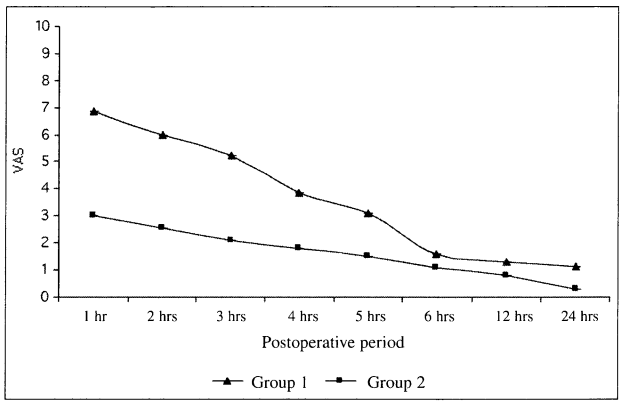

Figure 1. — Postoperative patient VAS data.

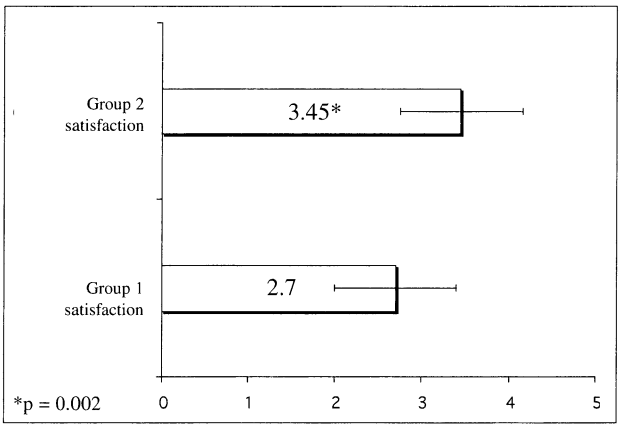

Figure 2. — Postoperative patient satisfaction.

The side-effects observed are shown in Table 7 and no statistical significance was found.

Postoperative patient satisfaction was assessed with group 2 having higher satisfaction than group 1 (3.45 and 2.7, respectively) (Figure 2).

Discussion

The clinician has multiple possibilities for the treatment of postoperative pain. Moreover, the choice of administration and dosage is very significant for successful therapy. Tramadol has been shown to be effective and safe for the treatment of postoperative pain [2]. The potential advantages of administering tramadol for postoperative pain relief include long duration of action and limited respiratory depressant effects [3, 6]. Tramadol is a weak μ-opioid receptor agonist and also causes inhibition of neuronal noradrenalin uptake and seratonin release [7-9] which enhance analgesia that occurs 1-2 hours after IV administration. Therefore tramadol should preferably be given during surgery since administration after inhalation anaesthesia has been shown to provide inadequate postoperative pain relief [3, 6, 10]. We wanted to determine the efficacy of tramadol IV infusion versus epidural for postoperative pain relief in gynaecologic cancer operations, thus we preferred to give tramadol infusion during surgery. Continuous administration of an analgesic by means of infusion is easier to implement especially with PCA equipment. A disadvantage of continuous administration is the possible danger of overdosing, especially if there is no PCA equipment. We used 10 mg/h tramadol infusion in both groups. If the dosage was not sufficient for pain relief, the patients could add more analgesic set to a limited drug dosage with the PCA pump system.

There is varying opinion on the significance of the initial bolus before the commencement of PCA therapy. Lehmann *et al.* reported only a slight influence on subsequent analgesic requirements by 50 or 100 mg tramadol [11]. Hackl *et al.* found that the high initial bolus dose did not significantly change the total dose [12]. We preferred the use of a 20 mg bolus dose of tramadol in each group five minutes before induction and then started the infusion.

In PCA the amount of the demand bolus is of considerable importance. If boluses are too small, the patients are unable to achieve therapeutic levels by increasing the demand and pain relief can not be achieved. If boluses are too high, risk of opioid side-effects is increased. Consequently, we selected a 20 mg demand dose which was far lower than a dose with danger of side-effects.

Postoperative pain is influenced by the method of anaesthesia used and type and site of the operation [13, 14]. Therefore we used a standardized anaesthesia proce-

dure, and confined the study to comparable standard gynaecological cancer operations. Cardiovascular parameters throughout the peroperative period were slight and insignificant between groups. Significant bradycardia or systolic arterial pressure did not decrease. Respiratory rates and oxygen saturation were followed-up and no depression was found in either group.

Tramadol is reputed to cause less respiratory depression than morphine [2, 3]. We found no respiratory depression or any significant decrease in oxygen saturation in this study.

Significant pain relief was reported by both groups in the first hour. The pain situation improved more rapidly in group 2 than in group 1. After six hours, the values got closer in both groups. In contrast to tramadol consumption the VAS was significantly lower in the epidural group. Tramadol consumption was lower in the epidural group with a lower demand rate. Intravenously administered tramadol is equivalent to pethidine [3], but its analgesic potency is only 5-10 times less than morphine [1]. Tramadol administered epidurally was one-third as potent as morphine in patients following abdominal surgery [6]. A significantly better assessment of the quality of analgesia was revealed in group 2. Patient satisfaction is shown in Figure 2.

Postoperative analgesia was achieved in both groups but the quality of analgesia was found to be significantly higher in the epidural group. Thus, the therapeutic goal was achieved more rapidly in the epidural group postoperatively. The VAS got closer in both groups six hours postoperatively as well as 12 hours and the demand rate decreased and lower side-effects occurred in the epidural group.

Nausea and vomiting can be seen in 20-80% of cases using opioids epidurally and intravenously [15, 16]. Vincent *et al.* found that nausea and vomiting have a lower incidence when used epidurally [17]. We admitted metoklopramid at the end of anaesthesia to prevent nausea and vomiting. We found more nausea and vomiting in the intravenous group due to higher tramadol consumption. It may be because the epidural way decreased the consumption of tramadol in group 2 with IV tramadol. Delilkan *et al.* found that nausea and vomiting depend on the increased dosages when the dosage is high and tramadol is used epidurally [18].

We conclude that epidural or intravenous infusion of tramadol is efficient for postoperative pain relief, but epidural tramadol is safe and has a better VAS as well as patient satisfaction score than intravenous tramadol. We may say that epidural tramadol infusion may be choosen for postoperative pain relief in gynaecological cancer operations.

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