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SHORT COMMUNICATION

INFLUENCE OF PRE- OR INTRAOPERATIONAL USE OF TRAMADOL (*PREEMPTIVE OR PREVENTIVE ANALGESIA*) ON TRAMADOL REQUIREMENT IN THE EARLY POSTOPERATIVE PERIOD

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Influence of pre- or intraoperational use of tramadol (preemptive or preventive analgesia) on tramadol requirement in the early postoperative period. J. WORDLICZEK, M. BANACH, J. GARLICKI, J. JAKOWICKA-WORDLICZEK, J. DOBROGOWSKI. Pol. J. Pharmacol., 2002, 54, 693–697.

The aim of this study was to assess the influence of *iv* tramadol on opioid requirement in the early postoperative period. The subjects were 90 patients scheduled for colon surgery (hemicolectomy) who received general anesthesia using the (N_2O/O_2) isoflurane technique. Thirty patients (group I) were administered 100 mg of tramadol *iv* before induction of general anesthesia (preemptive analgesia). Group II (30 patients) was administered 100 mg of tramadol *iv* immediately after peritoneal closure (preventive analgesia) and control group (30 patients) received 100 mg of tramadol *iv* immediately after operation. Following the operation, all patients were administered tramadol in the PCA-*iv* mode in order to treat postoperative pain. In the postoperative period, the following parameters were measured: pain intensity (using VAS), total consumption of tramadol, time until the first PCA activation, and frequency of side effects (drowsiness, nausea, vomiting).

In patients of groups I and II who had received preemptive or preventive analgesia, a significantly lower total consumption of tramadol, as compared with control group, was observed in the early postoperative period. However, the time until the first PCA activation was significantly shorter in group I as compared to the other two groups. No significant differences between the groups were found regarding pain intensity and frequency of side effects.

Key words: *Anaesthesia, preemptive analgesia, postoperative pain, opioids, tramadol*

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INTRODUCTION

The flow of nociceptive information in the perioperative period has a bi-phased character. The first phase is directly connected with nociceptive stimulation that accompanies injuries brought about by surgical procedures. The second phase, manifesting itself in the postoperative period, is the result of inflammatory responses related to this injury and is caused by the first-phase-changes in nociceptive structures of the spinal cord. The aim of preemptive analgesia is to prevent or inhibit the first phase and thus to protect the CNS from increased noxious stimulation during surgery [5, 6].

A modification of preemptive analgesia as one approach to postoperative pain management is *preventive analgesia.* This method is characterised by the administration of analgesics immediately before surgical closure. In the case of laparotomy, for instance, the analgesic is administered immediately after peritoneal closure.

Tramadol is an opioid analgesic widely used in anaesthesiology and particularly suitable for the induction of preemptive analgesia. This feature is related to tramadol's unusual mode of action: as an opioid it has a lower affinity for the μ-opioid receptor than morphine resulting in an analgesic potency which is 10 times weaker than that of morphine but similar to that of pethidine. Furthermore, only 40% of tramadol's analgesic effect is antagonized by naloxone, pointing to an additional non-opioid mechanism which contributes to tramadol's overall analgesic effect [7]. This second mechanism is related to the activation of the descending antinociceptive system and consists in both an inhibition of the re-uptake mechanisms for noradrenaline and serotonin (5-HT), and an increased release of 5-HT [1, 3, 7].

The aim of the present study was to assess the influence of *iv* tramadol-administered before general anesthesia (*preemptive analgesia*), immediately after peritoneal closure (*preventive analgesia*) or immediately after surgery – on tramadol requirement in the early postoperative period.

MATERIALS and METHODS

Patients scheduled for elective colon surgery (hemicolectomy) participated in the study. This operation was chosen due to its uniform duration, course of surgery and magnitude of surgical trauma, which allows for repeatable data to be collected. None of the patients had severe hepatic, renal, cardiovascular, or psychological disorders.

A day before surgery, the patients were instructed how to complete the visual analog scale (VAS) interview and to use the patient-controlled analgesia (PCA) pump. Patients who could not rate the VAS score or use the PCA pump were excluded from the study.

Each patient was premedicated with atropine, 0.01 mg/kg, and midazolam 0.04 mg/kg.

All patients received general anesthesia with inhalation of 1–2 vol% of isoflurane in 30% oxygen-70% nitric gas mixture and intravenous vecuronium (0.08 mg/kg/h), after tracheal intubation they were given intravenous propofol (2 mg/kg), and vecuronium (0.16 mg/kg). At the completion of skin closure, muscle relaxation was reversed with atropine, 0.01 mg/kg, and neostigmine, 0.03 mg/kg, and patients were extubated after confirmation of absence of hypercapnia (high end-tidal carbon dioxide concentration), or decreased respiratory rate (< 12 breaths/min).

Patients were randomly allocated into three groups (see Tab. 1).

Table 1. Data of patients included in the study

	N (patients)	Sex F/M	Age	Body weight (kg)	Duration of surgery (min)	Duration of observation (h)
I Group	30	12/18	44.8 ± 11.2 (20–59)	70.0 ± 7.8 (61–88)	171.5 ± 32.1 (90–220)	19.2 ± 1.5 (16–22)
II Group	30	14/16	43.3 ± 9.6 (26–57)	71.2 ± 9.3 (54–84)	179.8 ± 29.1 (100–220)	19.7 ± 1.8 (17–23)
Control group	30	15/15	44.0 ± 10.4 (22–57)	70.8 ± 6.52 (58–80)	175.8 ± 30.6 (100–225)	19.4 ± 1.5 (17–22)

30 patients (I group) were administered 100 mg of tramadol *iv* 15 minutes before induction of general anesthesia. The patients of II group were administered 100 mg of tramadol *iv* immediately after peritoneal closure. In order to determine the influence of the inhibition of phase II (inflammatory response in the postoperative period) on nociceptive stimulation, patients in control group (30 patients) received 100 mg of tramadol *iv* immediately after operation.

Following surgery, the patients were transferred to the recovery room and postoperative analgesia was administered as PCA to enable the patients to self-administer required doses of analgesics. After activation of PCA, all patients were given boluses of 20 mg of tramadol with a lockout time of 5 min.

The total tramadol requirement was determined for all patients in the early postoperative period. The level of intensity of postoperative pain was also measured using the Visual Analogue Scale (VAS) with read outs at six times: VAS_R – pain intensity which made the patient activate the PCA system, VAS_1 – 2 h following the operation, VAS_2 – 4 h following the operation, VAS_3 – 8 h following the operation, VAS_4 – 12 h following the operation, and VAS_5 – in the morning of the day following the operation. The latency of the first PCA activation and frequency of adverse effects (drowsiness, nausea, vomiting) was also measured for all patients. The clinical trial was carried out according to the protocol approved by the Ethics Commission of the Collegium Medicum of the Jagiellonian University, Kraków, Poland.

The results were assessed by an analysis of variance (ANOVA). Intergroup differences were analyzed by Duncan's multiple-range test. Clinical data are presented as means ± SD.

RESULTS

Tramadol requirements in the early postoperative period were significantly lower ($p < 0.05$) in patients who were administered tramadol in the preemptive analgesia (I group) or preventive analgesia approach (II group) as compared with the patients in the control group (Fig. 1). The values of the total dosages of tramadol were calculated without a dose of 100 mg of tramadol, which group I patients received to induce "preemptive analgesia" effect, group II patients to induce "preventive anal-

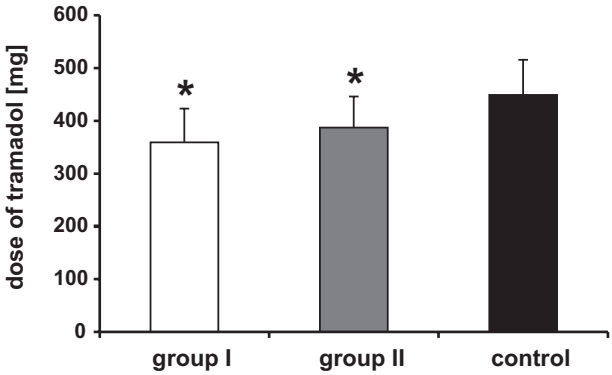

Fig. 1. The influence of tramadol in various models of analgesia on the total opioid requirement in the early postoperative period. * significant difference with respect to control group ($p < 0.01$)

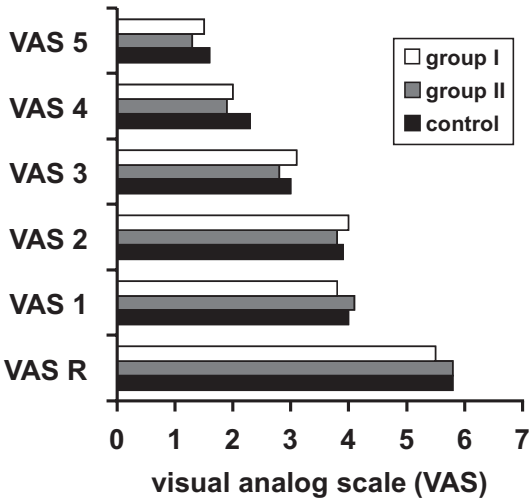

Fig. 2. The influence of tramadol on postoperative pain intensity. No statistically significant differences were found between the analyzed groups

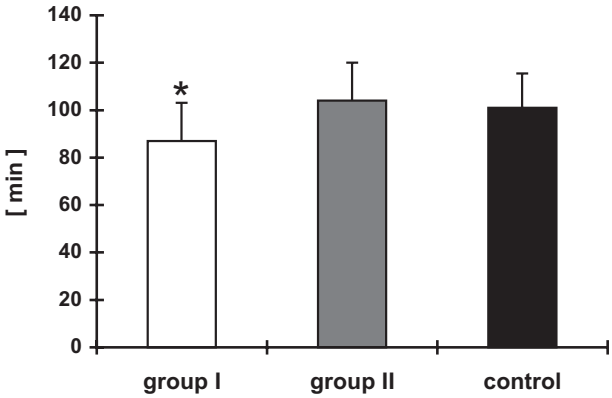

Fig. 3. The influence of tramadol on the latency of first PCA activation. * significant difference with respect to group II and control group ($p < 0.01$)

gesia" effect and in control group to inhibit the development of phase II of inflammatory response.

However and as can be seen from Figure 2, the postoperative pain intensity did not statistically differ between the three study groups. These data indicate that patients in group I and II self-administered smaller doses of tramadol to achieve a similar level of analgesia (Fig. 2).

It was also established that the time (min) elapsed between the end of the operation and the first PCA activation was significantly shorter in I group as compared with groups II and control (Fig. 3).

Adverse effects

The patients undergoing surgery developed postoperatively the following adverse reactions: nausea, vomiting, and drowsiness. Their frequency is presented in the Table 2.

Table 2. The influence of tramadol on the frequency (%) of adverse effects in postoperative period

Group	Drowsiness	Nausea	Vomiting
I	23.3%	23.3%	6.6%
II	26.6%	23.3%	6.6%
control	30%	30%	10%

No significant differences in frequency of adverse effects were observed among groups under investigation. However, their frequency was highest in control group, most probably due to the significantly higher doses of tramadol administered to these patients. Also, in two patients from this group, intensity of nausea and vomiting was moderate, and in the remaining subjects from other groups intensity of adverse events was mild.

DISCUSSION

The use of tramadol, that possesses bi-directional action, in *preemptive analgesia* opens up opportunities for a successful inhibition of the development of the nociceptive process as well as its consequences in the perioperative period. This has been confirmed in the experimental and clinical observations on the effect of preemptive analgesia induced by the drugs activating noradrenergic and serotoninergic system [11] which suggest that not only opioids but also drugs activating descending antinociceptive system are able to inhibit development of central sensitization.

In the present clinical study we examined the influence of tramadol administered both in the preoperative period (preemptive analgesia, group I), immediately following peritoneal closure (preventive analgesia, group II), as well as after extubation (inhibiting the development of phase II, control group) on the overall analgesic requirement in the postoperative phase.

No significant differences regarding pain intensity were observed during the study, which corresponds with the findings of other authors [4, 8]. However, a significantly shorter time interval between the completion of the surgery and the first PCA activation in group I compared to groups II and control is probably related to the action of tramadol used in the groups II and control towards the end or after the completion of the surgery. Similar observations were made by Hartjen et al. [4]. Patients in groups I and II demonstrated a significantly lower opioid requirement, which confirms the possibility for preemptive and preventive tramadol to inhibit the activation of the sensitization process in phase I of nociception. This is confirmed by other authors who used opioids to induce preemptive analgesia [8, 10]. The absence of such an effect in control group of patients confirms the results of experimental studies in that the inhibition of phase II of nociception may not significantly affect the development of the process of sensitization. The increased opioid requirement in patients subjected to preventive analgesia as compared to group I is probably related to the fact that nociceptive processes had already been initiated by the surgical procedure. Consequently, their inhibition would have required higher doses of tramadol. Nonetheless, it must be stressed that owing to the bi-directional action of tramadol, its use in modulating the nociceptive process opens new possibilities in a therapeutic modification of the development of sensitization processes in the perioperative period.

The frequency of side effects did not significantly differ between the groups. The 23.3–30% of patients complained about nausea, which is, again, similar to the values reported elsewhere [9, 12]. However, the ratio of patients who vomited following the surgery was lower (6.6–10%) from that observed in other studies [2], although other authors

reported such effect only in 5% of patients under investigation [4, 9].

We conclude that the pre- or intraoperational use of tramadol (*preemptive or preventive analgesia*) significantly reduces opioid requirement in the early postoperative period, confirming the possibility that tramadol used in this way may inhibit the activation of sensitization processes connected with phase I of the nociceptive information flow. The absence of such effects in patients from control group, indicates that the inhibition of already developed phase II does not significantly affect the nociception processes which follows the surgery.

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REFERENCES

1. Bamigbade T.A., Davidson C., Langford R.M., Stamford J.A.: Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus. Brit. J. Anaesth., 1997, 79, 352.
2. Bamigbade T.A., Langford R.M.: The clinical use of tramadol hydrochloride. Pain Rev. 1998, 5, 155.
3. Driessen B., Reimann W., Giertz H.: Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro. Brit. J. Pharmacol., 1993, 108, 806.
4. Hartjen K., Fisher M.V., Mewes R., Parvicini D.: Präventive Schmerztherapie. Anästhesist 1996, 45, 538–544.
5. Katz J., Kavanagh B.P., Sandler A.N.: Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. *Anesthesiology* 1992; 77: 439–446.
6. Kissin I.: Preemptive analgesia. *Anesthesiology* 2000; 93: 1138–1143.
7. Raffa R.B., Friderichs E., Reimann W., Shank R.P., Codd E.E., Vaught J.L.: Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an "atypical" opioid analgesic. J. Pharmacol. Exp. Ther. 1992, 260, 275–285.
8. Richmond C.E., Bromley L.M., Woolf C.J.: Preoperative morphine pre-empts postoperative pain. Lancet 1993, 342,73–75.
9. Vickers M.D., Paravicini D.: Comparison of tramadol with morphine for post-operative pain following abdominal surgery. Eur. J. Anaesth. 1995, 12, 265–271.
10. Woolf C.J., Chong M-S.: Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anest. Analg. 1993, 77, 362–379.
11. Wordliczek J., Banach M., Dorazil M., Przewłocka B.: Influence of doxepine used in preemptive analgesia on the nociception in the perioperative period. Experimental and clinical study. Pol. J. Pharmacol., 2001, 53, 253–261.
12. Wordliczek J., Krzyżanowska-Kula T., Strzelewicz D.: Intravenous patient-controlled analgesia for pain relief after cholecystectomy. A comparison of tramadol and pethidine. Anaesth. Inten. Ter. 1994, 26, 273–277.

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