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Effect of Analgesia Administration Timing on Early Post-operative Period Characteristics: a Randomized, Double-blind, Controlled Study

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This study investigated the effect of time of analgesia administration in 64 patients undergoing total abdominal hysterectomy. Patients received standard general anaesthesia and were divided randomly into two equal groups. At the time of fascia closure, patients in the intra-operative (Iop) group received 0.5 mg/kg pethidine intravenously. On arrival in the post-anaesthesia care unit, the same dose of pethidine was given to patients in the post-operative (Pop) group. All patients then used a patient-controlled analgesia pump to administer pethidine analgesia as required. Times to extubation, response to verbal stimulation and orientation, post-operative pain scores and analgesic consumption were recorded. Times to extubation and response to verbal stimulation were significantly longer in the Iop group. Pain scores, analgesic consumption and additional analgesic requirements were significantly higher in the Pop group in the first 2 h post-operatively. In conclusion, intra-operative administration of pethidine provided better pain management than post-operative administration.

KEY WORDS: Pethidine; Pain management; Timing of analgesia; Post-operative period

Introduction

Pre-emptive and preventive analgesia are frequently used to prevent and reduce post-operative pain and to reduce analgesic requirements.[1] Pre-emptive analgesia involves giving analgesia before surgery, with the aim of blocking the central sensitization of the nervous system as a result of the surgical incision and inflammatory damage.[2] Preventive analgesia, which may be confused with pre-emptive analgesia, is the commencement of analgesia before completion of surgery[3] or during the early post-operative period.[4] The timing of administration may be important in determining the effects of peri-operative analgesia.

Opioids have good analgesic efficacy, are low cost and are widely used for the treatment of post-operative pain. In particular, the synthetic opioid pethidine is often used for patient-controlled analgesia

because it has a short onset time and few side-effects.[5,6]

This randomized, double-blind, controlled study aimed to investigate the effect of administration time of patient-controlled analgesia (PCA) with intravenous pethidine on anaesthetic recovery, pain scores and analgesic requirements in patients undergoing elective total abdominal hysterectomy with or without bilateral salpingo-oophorectomy.

Patients and methods

PATIENTS

This study involved patients classified as American Society of Anesthesiologists physical status class I or II and undergoing elective total abdominal hysterectomy with or without bilateral salpingo-oophorectomy. Patients with a chronic pain disorder, psychiatric illness, hepatic or renal disorders, a history of alcohol or drug abuse, convulsions, opioid allergy, non-steroidal anti-inflammatory drug treatment or morbid obesity were excluded from the study.

During the pre-anaesthetic evaluation on the day before surgery, patients were shown how to use the PCA pump and were instructed on how to use the visual analogue scale pain score at rest (VAS-R)[7] to evaluate pain intensity (0, no pain; 10, worst pain).

Approval for the study was obtained from the Medical Faculty Drug Research Ethics Committee at Dokuz Eylül University Medical School, and written informed consent was given by all the study participants.

ANAESTHESIA

All patients were pre-medicated with 0.15 mg/kg diazepam orally at night and 2 h before surgery. General anaesthesia was induced with intravenous thiopental 3 – 5 mg/kg, fentanyl 2 µg/kg and vecuronium 0.1 mg/kg. Maintenance of anaesthesia was achieved with sevoflurane in a gas mixture of 50% oxygen and 50% nitrous oxide. No additional fentanyl was given. During surgery, the electrocardiogram, peripheral oxygen saturation, non-invasive systemic blood pressure and end-tidal carbon dioxide partial pressure were monitored (Hewlett Packard, M1166A® Viridia CMS, Andover, MA, USA). Sevoflurane was discontinued at the end of skin closure. All patients were extubated following administration of atropine and neostigmine for the reversal of residual paralysis.

During the recovery period, all patients received oxygen at a concentration of 2 – 4 l/min via a face mask. Anti-emetic treatment (10 mg metoclopramide intravenously for a period of 6 h) was prescribed for patients who experienced post-operative nausea and vomiting.

ANALGESIA

During closure of the fascia, patients were randomly allocated using a sealed envelope method into one of two groups: the intra-operative pethidine group (Iop) or the post-operative pethidine group (Pop). The PCA pump (Abbott Life Care PCA Plus Infuser, Abbott Laboratories, North Chicago, IL, USA) was set to deliver a loading dose of 0.5 mg/kg pethidine (500 mg in 100 ml 0.9% NaCl) and bolus doses of 10 mg pethidine with a lock-out time of 10 min without any background infusion. The limit dose of pethidine was 150 mg over 4 h.

For patients in the Iop group, the intravenous loading dose of pethidine was administered using the PCA pump during the closure of the fascia. For patients in the Pop group, the intravenous loading dose of pethidine was administered via the PCA pump in the post-anaesthesia care unit

(PACU). The intravenous loading dose of pethidine was administered in both cases by an anaesthetist who was not aware of the solution content.

All patients then used the PCA pump to administer pethidine analgesia as required.

ASSESSMENT OF POST-OPERATIVE PAIN AND ANALGESIA USE

The time periods from discontinuation of sevoflurane to extubation (extubation time, ET), to responding to verbal stimulation (verbal stimulation time, VT) and to orientation to place and time (orientation time, OT) were recorded.

Post-operative VAS-R scores, analgesic demands and consumption, side-effects and Aldrete scores[8] were assessed after 0, 15, 30, 60 and 120 min in the PACU. Patients who had VAS-R scores > 5 were given 10 mg additional bolus doses of pethidine. At the end of 120 min, those who had Aldrete scores > 8 were discharged from the PACU. Post-operative VAS-R scores, discharge criteria and opioid-related side-effects were assessed by a researcher who was blind to the patient's group.

Pain was re-assessed after 6, 12, 24 and 48 h by the acute-pain team. Post-operative PCA administration was discontinued 48 h post-operatively.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS® 11.0 for Windows (SPPS, Chicago, IL, USA). Results were given as the mean ± SD. Demographic data and recovery characteristics were compared using the Student's *t*-test. Pain scores and analgesic consumption were analysed using repeated measures analysis of variance with Bonferroni correction within the groups and using the Student's *t*-test between the groups. χ^2 and Fisher's exact tests were used for the comparison of adverse effects. A *P*-value < 0.05 was considered to be statistically significant.

Results

A total of 64 patients aged between 18 and 65 years of age were included in the study, 32 in the Iop group and 32 in the Pop group. One patient from each group was excluded because of technical reasons; therefore data from a total of 62 patients were analysed.

The sample size of the study was based on data from a previous study.[9] The power of the study was 80%, and a 30% reduction in the VAS-R scores in the Iop group was considered significant, with an α error of 0.05 and a β error of 0.2.

There were no differences in the demographic data or the duration of surgery between the groups (Table 1). ET and VT were significantly longer in the Iop group (Table 1), but no difference was seen in OT between the two groups (Table 1).

During the time spent in the PACU, the VAS-R scores were significantly higher in the Pop group (Fig. 1).

The number of analgesic demands between 15 and 30 min post-operatively was significantly lower in the Iop group (3.84 ± 4.62) compared with the Pop group (10.39 ± 14.89) ($P < 0.05$). Cumulative PCA demands were also significantly lower in the Iop group than in the Pop group (67.89 ± 37.21 versus 111.10 ± 83.66, respectively; $P < 0.05$). Although the number of PCA deliveries was higher in the Pop group (36.00 ± 18.56) than in the Iop group (32.13 ± 12.86), this difference was not statistically significant.

During the time spent in the PACU, there were significant differences in pethidine consumption between the two groups (Fig. 2). Cumulative pethidine consumption was significantly lower ($P < 0.05$) in the Iop group than in the Pop group after the first 24 h

TABLE 1:
Demographic data, duration of surgery and times to extubation, response to verbal stimulation and orientation in patients undergoing total abdominal hysterectomy and receiving a loading dose of pethidine either intra-operatively (Iop) or post-operatively (Pop)

	Iop group (n = 31)	Pop group (n = 31)
Age (years)	48.48 ± 7.57	46.61 ± 6.01
Weight (kg)	69.48 ± 10.62	67.90 ± 8.52
Duration of surgery (min)	88.10 ± 21.93	79.84 ± 24.23
Extubation time (min)	10.55 ± 5.53[a]	7.58 ± 4.50
Verbal stimulation response time (min)	13.61 ± 6.11[a]	10.03 ± 5.12
Orientation time (min)	19.03 ± 7.49	16.19 ± 5.26

Values are mean ± SD.
[a]$P < 0.05$.

(331.29 ± 128.69 mg versus 391.58 ± 95.11 mg, respectively). Although total pethidine consumption over the first 48 h was lower in the Iop group than in the Pop group, this did not reach statistical significance (372.25 ± 151.36 mg versus 421.58 ± 105.49 mg, respectively).

Additional pethidine consumption during the first 2 h was significantly higher ($P < 0.05$) in the Pop group (31.29 ± 17.65 mg) than in the Iop group (6.45 ± 11.41 mg).

The Aldrete scores during the whole period spent in the PACU showed no significant differences between the two

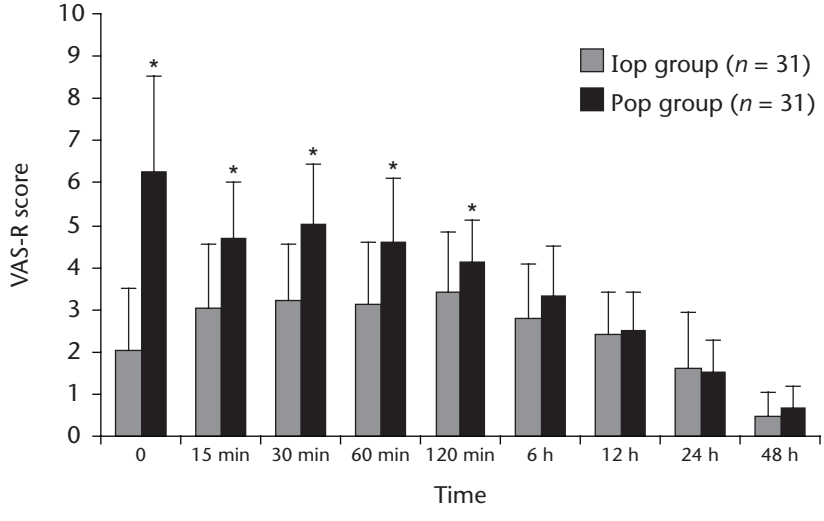


FIGURE 1: Post-operative visual analogue scale at rest (VAS-R) scores (mean ± SD) in patients undergoing total abdominal hysterectomy and receiving a loading dose of pethidine either intra-operatively (Iop) or post-operatively (Pop). *$P < 0.05$

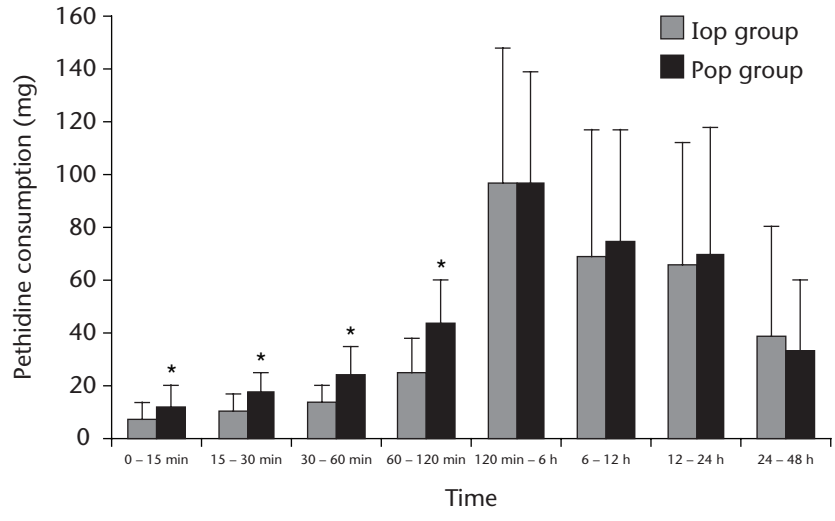


FIGURE 2: Post-operative pethidine consumption (mean ± SD) in patients undergoing total abdominal hysterectomy and receiving a loading dose of pethidine either intra-operatively (Iop) or post-operatively (Pop). *$P < 0.05$

groups. Nausea and vomiting were the only side-effects in the post-operative period; the incidence was similar in the two groups, with nausea occurring in 19 patients in the Iop group and 21 patients in Pop group, and vomiting occurring in three patients in both groups. No other untoward reactions were observed.

Discussion

Katz and McCartney[1] reviewed studies of pre-emptive and preventive analgesia and classified the treatments given according to the timing of the analgesic administration. The timings used in the present study correspond to their fourth (Pop) and seventh (Iop) treatment combinations. The efficacy of the preventive administration of opioids is still controversial.[10]

In our study, ET and VT were found to be significantly longer in the Iop group, but there was no significant difference between the two groups in terms of OT. Delayed recovery seemed to be associated with intra-operative pethidine, but patients in the Iop group had lower VAS-R scores in the PACU during the first 2 h post-operatively.

In this study, we used the recommended intravenous loading dose of pethidine (0.5 mg/kg).[11] Cumulative PCA demands were significantly higher in the Pop group, but cumulative pethidine consumption was not different between the two groups. This may be because the same PCA settings were used for both groups; there might have been a difference in pethidine consumption between the two groups if the lock-out interval was shorter. The 10-min lock-out time was chosen based on the results of previous studies, which had found higher incidences of side-effects with shorter lock-out times.[12]

Wong *et al.*[13] compared different timings for the administration of a morphine loading dose (intra-operative versus post-operative) for ambulatory surgery to determine whether there was an effect on

post-operative nausea or vomiting, quality of analgesia and morphine consumption. In contrast to our results, they reported that pain scores were higher in the Pop group in the PACU only during the first 15 min of the recovery period. In a randomized study, Pang *et al.*[14] observed that there were fewer side-effects in those receiving an intra-operative intravenous 5 mg/kg tramadol loading dose compared with those receiving post-operative PCA, without any significant differences in post-operative analgesia quality. Wordliczek *et al.*[3] found that administration of intravenous 100 mg tramadol pre-operatively (pre-emptive analgesia) or intra-operatively (preventive analgesia) reduced tramadol consumption and VAS-R scores in the post-operative period, which is consistent with the results of our study. They also observed that there were no significant differences in side-effects between these two groups or those who received post-operative tramadol. Pjevic *et al.*[15] administered intravenous 1 mg/kg pethidine in the pre-operative or intra-operative period and found no significant differences between the groups in terms of post-operative pain scores or analgesic consumption. In the present study, we found lower VAS-R scores in the Iop group in the first 2 h post-operatively, which may be due to the prevention of sensitization.

In our study, nausea and vomiting occurred as side-effects of pethidine administration; however, there was no significant difference between the groups in the incidence of these side-effects after 48 h. These findings are consistent with the results of Wong *et al.*[13] and Wordliczek *et al.*[3]

In conclusion, although it causes a prolongation in the recovery time, administration of intravenous pethidine in the intra-operative period provides better pain management and reduces analgesic requirements, especially in the first 2 h post-operatively.

Conflicts of interest

No conflicts of interest were declared in relation to this article.

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