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Prevention of postoperative nausea and vomiting by continuous infusion of subhypnotic propofol in female patients receiving intravenous patient-controlled analgesia

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In this prospective, randomized, double-blind, placebo-controlled study, the use of continuous subhypnotic propofol infusion as an antiemetic in fentanyl intravenous patient-controlled analgesia (i.v. PCA) was investigated during the first 24 h after surgery. One hundred female patients, ASA I–II, aged 20–71 yr, undergoing major gynaecological or orthopaedic surgery, were included. Either propofol 10 mg or placebo (1 ml of Intralipid) was given and one of the following five regimens was maintained for 24 h: propofol 5, 10, 15 or 20 μg kg^{-1} min^{-1} or Intralipid 1 ml h^{-1} as a placebo. Fentanyl i.v. PCA was started in the postanaesthesia care unit for postoperative analgesia. Significantly more of the patients given propofol 15 and 20 μg kg^{-1} min^{-1} experienced no nausea or vomiting compared with those given placebo (65% and 70% versus 25%; $P<0.05$). Patients given propofol 20 μg kg^{-1} min^{-1} reported more sedation than those in the other groups 4 h after surgery ($P<0.05$).

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Postoperative nausea and vomiting (PONV) is one of the most common complications following anaesthesia and surgery. Although various antiemetics have been evaluated for the management of PONV, none of the currently available prophylactic antiemetic regimens are entirely successful.

The direct and indirect antiemetic effects of propofol are well known. As an anaesthetic, propofol has been associated with a lower incidence of PONV.[1] Propofol infusion in subhypnotic doses has been used successfully to manage chemotherapy-induced emesis.[2] Its efficacy for the prevention of PONV, however, has not been proven conclusively.[3,4]

This prospective, randomized, double-blind, placebo-controlled study was undertaken to investigate whether continuous subhypnotic propofol infusion would prevent PONV in female patients receiving fentanyl i.v. PCA and to determine the optimal infusion rates of propofol.

Table 1 Patient characteristics, incidence of post-operative nausea and vomiting (PONV), requirement for rescue antiemetics during the first 24 h, and sedation scores 4, 8 and 24 h after surgery. Values are mean (SD) when appropriate. *Significantly different from placebo ($P<0.05$); n.s.=no significant difference. Total fentanyl consumption dose includes i.v. PCA dose only. G=gynaecological surgery (total abdominal hysterectomy); O=orthopaedic surgery (posterior spinal fusion with instrumentation)

		Propofol				
	Placebo	**5 μg**	**10 μg**	**15 μg**	**20 μg**	***P* value**
n	20	20	20	20	20	
Age (yr)	52 (11.7)	49 (14.8)	46 (12.6)	48 (8.6)	50 (12.0)	n.s.
Weight (kg)	54 (5.3)	56 (9.2)	59 (6.4)	56 (6.8)	55 (5.7)	n.s.
Duration of anaesthesia (min)	181 (90.7)	182 (64.8)	177 (68.0)	171 (79.4)	175 (72.2)	n.s.
Total fentanyl consumption (μg)	413 (241)	585 (362)	537 (280)	514 (208)	712 (445)*	0.049
Surgery (*n*) (G/O)	9/11	9/11	9/11	9/11	10/10	n.s.
PONV (*n*(%))						
No symptoms	5 (25)	8 (40)	9 (45)	13 (65)*	14 (70) *	0.001
Nausea only	4 (20)	6 (30)	8 (40)	3 (15)	5 (25)	
Vomiting	11 (55)	6 (30)	3 (15)	4 (20)	1 (5)	
Rescue antiemetics (*n* (%))	5 (25)	2 (10)	3 (15)	1 (5)	0 (0)	n.s.
Sedation score						
4 h	1.15 (0.75)	1.30 (0.66)	1.30 (0.73)	1.50 (0.61)	1.75 (0.44)*	0.043
8 h	1.00 (0.73)	1.20 (0.77)	1.15 (0.81)	1.35 (0.75)	1.45 (0.76)	n.s.
24 h	0.30 (0.57)	0.55 (0.60)	0.50 (0.69)	0.60 (0.75)	0.55 (0.69)	n.s.

Methods and results

One hundred female patients (ASA I–II, aged 20–71 yr, weight 43–74 kg) undergoing either elective major gynaecological or orthopaedic surgery were studied. Patients undergoing different types of surgical procedure were distributed equally among the groups to minimize bias. Institutional ethics committee approval was obtained. Written informed consent was obtained before enrolment.

Patients who had significant systemic diseases, those who had vomited or received antiemetics within 24 h before surgery, and those with known allergy to propofol or a history of epilepsy were not included. Also excluded were those with high risk factors such as a previous history of PONV or migraine, or women who were menstruating.

On the day before surgery, patients and their care-givers were instructed in the use of an APII PCA pump (Baxter Healthcare Co., Deerfield, IL, USA) and in the use of the nausea/vomiting and sedation score card. They were told to ask for rescue antiemetics when PONV occurred. One hour before surgery, midazolam 3–5 mg and glycopyrrolate 0.2 mg were given intramuscularly. Anaesthesia was induced with thiopental 5 mg kg^{-1} i.v. and fentanyl 2–3 μg kg^{-1}, and maintained with enflurane, 50% nitrous oxide and oxygen. All received vecuronium 0.1 mg kg^{-1} to facilitate tracheal intubation and for subsequent intraoperative neuromuscular blockade. At the end of surgery, this was reversed with pyridostigmine 10 mg and glycopyrrolate 0.2 mg i.v.

Medication was blinded and randomized by our pharmacy, which delivered covered and coded vials of propofol or Intralipid. After patients had regained consciousness in the recovery room, a bolus of Intralipid 1 ml or propofol (Pofol; Je-Il Pharmaceutical Co., Seoul, Korea) 10 mg was given intravenously followed by continuous infusion of intralipid as a placebo or propofol using an infusion pump. Those given propofol boluses were randomly allocated to receive one of four infusion regimens for 24 h: continuous propofol infusion at 5, 10, 15 or 20 μg kg^{-1} min^{-1}.

All patients received fentanyl i.v. as postoperative analgesia via another PCA pump. The fentanyl concentration was 20 μg ml^{-1}, total volume 100 ml and bolus dose 20 μg; there was no basal infusion. The lockout interval was 6 min.

Droperidol 1.25 mg i.v. was to be administered promptly as a rescue antiemetic when requested. Patients and their care-givers were given score cards and asked to record the occurrence of nausea and vomiting. The investigator, blinded to the study drugs, verified the PONV episodes 4, 8 and 24 h after surgery and recorded sedation scores and other adverse side effects. Total fentanyl consumption during the first 24 h after surgery was recorded at the end of the study period. Pain scores were not measured in this investigation.

PONV was assessed on a three-point scale: 0=no symptoms, 1=only nausea, 2=vomiting. The highest score reported during the study determined the category to which a patient was allocated. Thus, patients who experienced both nausea and vomiting were included in the vomiting category. Sedation was evaluated on a five-point scale: 0=awake, 1=drowsy, 2=asleep but responds to verbal commands, 3=asleep but responds to physical stimulus, 4=unrousable.

Statistical analysis was performed with SPSS version 7.5 (SPSS Inc., Chicago, IL, USA). Discontinuous data were analysed using the chi-square test, and continuous data by one-way analysis of variance with Bonferroni correction for multiple comparisons between the study groups. A *P*-value of <0.05 was considered significant.

The results are presented in Table 1. All groups were comparable with regard to patient characteristics and type and duration of surgical procedures. Patients in the placebo group used significantly less fentanyl than those who received propofol 20 μg kg^{-1} min^{-1} ($P<0.05$). Sixty-five per cent of the patients who received propofol 15 μg kg^{-1} min^{-1} and 70% of those who received propofol 20 μg kg^{-1} min^{-1} experienced no nausea or vomiting, compared with 25% of those who received placebo ($P<0.05$). Power analysis indicated that the sample size used here, 20 patients in each group, would be adequate to detect a 40% decrease in PONV with 90% power and an α error of 0.05.

Patients receiving propofol 20 μg kg^{-1} min^{-1} reported more sedation than those receiving placebo 4 h after surgery ($P<0.05$). However, reported sedation levels did not differ significantly among the groups at 8 or 24 h. Other adverse effects, such as respiratory depression, were not observed.

Discussion

Patients undergoing major gynaecological or orthopaedic surgery with fentanyl i.v. PCA were chosen for this study because the incidence of PONV in this group is high.[5] Every attempt was made to match groups for factors known to affect the incidence of PONV, so it is highly likely that the observed differences between groups were mainly caused by the treatment.

Studies investigating the use of continuous subhypnotic propofol infusion for the prevention of PONV have produced conflicting results. Ewalenko and colleagues reported that subhypnotic propofol infusion at 1 mg kg^{-1} h^{-1} effectively reduced the incidence of PONV from 65% to 10% without untoward sedative or cardiovascular effects after thyroidectomy.[3] Montgomery and colleagues[4] used a similar propofol infusion regimen but were unable to demonstrate any specific antiemetic effect over placebo. Our study showed that propofol infusion significantly reduced the incidence of PONV from 75% to 30%, similar to the results of Ewalenko and colleagues.[3]

There might be a therapeutic range of propofol concentration that prevents PONV. It has been shown that propofol for anaesthesia is associated with less PONV than volatile agents, but that it reduced only early PONV.[1] In previous studies on the management of chemotherapy-induced emesis and prophylaxis of PONV, 1 mg kg^{-1} min^{-1} (17 μg kg^{-1} min^{-1}) has been used as the continuous subhypnotic dose of propofol infusion.[2] Recently, Gan and colleagues demonstrated that a plasma concentration of propofol at 343 ng ml^{-1} was associated with 50% reduction in postoperative nausea.[6] Simulations indicated that a bolus dose of 10 mg followed by an infusion at approximately 10 μg kg^{-1} min^{-1} are necessary to achieve this plasma concentration. Based on these reports, propofol infusion rates of 5–20 μg kg^{-1} min^{-1} were selected for this study.

In our study, the patients who received propofol 20 μg kg^{-1} min^{-1} were more sedated than those receiving placebo 4 h after surgery, even though none developed respiratory depression. This might have been related to residual sedative effects of inhalational anaesthetics and the concurrent use of fentanyl by PCA. Thus, continuous infusion of high dose propofol combined with opioids such as fentanyl should be carried out cautiously.

Fentanyl consumption in the placebo group was significantly less than that in the propofol 20 μg kg^{-1} min^{-1} group. We feel that this was mainly because patients resisted pressing the button on the PCA pump, being afraid of aggravating PONV induced by PCA use.

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