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SCIENTIFIC ARTICLE

Effects of a novel method of anesthesia combining propofol and volatile anesthesia on the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic gynecological surgery☆

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KEYWORDS
Postoperative nausea and vomiting;
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Abstract
Background: We investigated the effects of a novel method of anesthesia combining propofol and volatile anesthesia on the incidence of postoperative nausea and vomiting in patients undergoing laparoscopic gynecological surgery.
Methods: Patients were randomly divided into three groups: those maintained with sevoflurane (Group S, $n = 42$), propofol (Group P, $n = 42$), or combined propofol and sevoflurane (Group PS, $n = 42$). We assessed complete response (no postoperative nausea and vomiting and no rescue antiemetic use), incidence of nausea and vomiting, nausea severity score, vomiting frequency, rescue antiemetic use, and postoperative pain at 2 and 24 h after surgery.
Results: The number of patients who exhibited a complete response was greater in Groups P and PS than in Group S at 0–2 h (74%, 76% and 43%, respectively, $p = 0.001$) and 0–24 h (71%, 76% and 38%, respectively, $p < 0.0005$). The incidence of nausea at 0–2 h (Group S = 57%, Group P = 26% and Group PS = 21%, $p = 0.001$) and 0–24 h (Group S = 62%, Group P = 29% and Group PS = 21%, $p < 0.0005$) was also significantly different among groups. However, there were no significant differences among groups in the incidence or frequency of vomiting or rescue antiemetic use at 0–24 h.
Conclusion: Combined propofol and volatile anesthesia during laparoscopic gynecological surgery effectively decreases the incidence of postoperative nausea. We term this novel method of anesthesia ''combined intravenous-volatile anesthesia (CIVA)''.
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PALAVRAS-CHAVE
Náusea e vômito pós-operatórios;
Propofol;
Sevoflurano;
Anestesia geral;
Laparoscopia

Efeitos de um novo método de anestesia combinando propofol e anestesia volátil sobre a incidência de náusea e vômito no pós-operatório em pacientes submetidas à laparoscopia ginecológica

Resumo
Justificativa: Investigamos os efeitos de um novo método de anestesia, combinando propofol e anestesia volátil, sobre a incidência de náusea e vômito no período pós-operatório de pacientes submetidas à laparoscopia ginecológica.
Métodos: As pacientes foram randomicamente divididas em três grupos: manutenção com sevoflurano (Grupo S, n = 42), com propofol (Grupo P, n = 42) ou com a combinação de propofol e sevoflurano (Grupo PS, n = 42). Avaliamos as respostas completas (sem náusea e vômito no pós-operatório e sem uso de antiemético de resgate), incidência de náusea e vômito, escore de gravidade da náusea, freqüência de vômitos, uso de antiemético de resgate e dor no pós-operatório em 2 e 24 h após a cirurgia.
Resultados: O número de doentes que apresentou uma resposta completa foi maior nos grupos P e PS que no Grupo S em 0-2 h (74%, 76% e 43%, respectivamente, p = 0,001) e 0-24 h (71%, a 76% e 38%, respectivamente, p < 0,0005). A incidência de náusea em 0-2 h (Grupo S = 57%, Grupo P = 26% e Grupo PS = 21%, p = 0,001) e 0-24 h (Grupo S = 62%, Grupo P = 29% e grupo PS = 21%, p < 0,0005) também foi significativamente diferente entre os grupos. Porém, não houve diferença significativa entre os grupos em relação à incidência ou frequência de vômitos ou uso de antiemético de resgate em 0-24 h.
Conclusão: A combinação de propofol e anestesia volátil durante a laparoscopia ginecológica efetivamente diminui a incidência de náusea no pós-operatório. Denominamos este novo método de anestesia ''anestesia combinada intravenosa volátil (ACIV)''.
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Introduction

Volatile anesthetics exert cardioprotective effects mediated by the activation of adenosine triphosphate-sensitive potassium (KATP) channels in cardiac myocytes.[1,2] They also affect coronary vasodilation by activating KATP channels in vascular smooth muscle cells.[3,4] Therefore, the use of volatile anesthetics for clinical anesthesia may be beneficial in prevention of coronary artery disease.

Total intravenous anesthesia (TIVA) with propofol also has many advantages. It decreases the incidence of postoperative nausea and vomiting (PONV),[5,6] decreases cerebral blood flow and intracranial pressure,[7] and attenuates postoperative pain[8] and neuroendocrine stress response.[9]

Because of these benefits combined with the rapid onset and cessation of action, both volatile anesthetics and propofol are extensively used for clinical anesthesia.

We hypothesized that a novel method of anesthesia combining propofol and volatile anesthesia can provide the benefits of both while decreasing the disadvantages of each anesthetic. In this study, we investigated the effects of combined propofol and volatile anesthesia on the incidence of PONV in patients undergoing laparoscopic gynecological surgery.

Materials and methods

After obtaining approval for this study from the Ethics Committee on Human Studies of Tokushima University Hospital, written informed consent was obtained from all patients. All patients were scheduled for elective laparoscopic gynecological surgery (removal of ovarian tumors and cysts, adhesiolysis, myomectomy, salpingostomy, ovarian drilling and oophorectomy) under general endotracheal anesthesia, with an American Society of Anesthesiologists (ASA) physical status of I and II. The study's exclusion criteria were as follows: obesity (body mass index >33 kg/m^2); neurological, renal, or liver disease; and the use of drugs with antiemetic properties, including corticosteroids. Risk factors associated with PONV were recorded.

Patients were randomly assigned to one of the following three groups by the sealed envelope method: those maintained with sevoflurane (Group S), those maintained with propofol (Group P), and those maintained with combined propofol and sevoflurane (Group PS).

No preanesthetic medication was administered. All patients were monitored by electrocardiography, noninvasive arterial blood pressure measurement, pulse oximetry, capnography, and the bispectral index (BIS) monitoring. No nasogastric tubes were inserted. General anesthesia was induced with intravenous remifentanil, thiamylal (Group S) or propofol (Groups P and PS) and rocuronium. Anesthesia was maintained with remifentanil and sevoflurane, propofol, or combined propofol and sevoflurane in 2:1 air and oxygen.

In Group S, anesthesia was maintained with sevoflurane (end-tidal concentration approximately 1 minimum alveolar concentration). In Group P, anesthesia was maintained with an infusion of propofol (4–8 mg/kg/h). In Group PS, anesthesia was maintained with combined propofol (2 mg/kg/h) and sevoflurane (end-tidal concentration approximately 0.5 minimum alveolar concentrations). Sevoflurane concentration (Group S) and propofol infusion

Table 1 Patient demographics.

	Group S ($n=42$)	Group P ($n=42$)	Group PS ($n=42$)
Age (years)	38.9 ± 13.0	37.5 ± 13.0	40.0 ± 13.3
Height (cm)	157.6 ± 5.0	156.4 ± 5.1	157.5 ± 5.9
Weight (kg)	53.8 ± 6.9	51.8 ± 8.2	53.6 ± 9.6
MABP at admittance (mmHg)	94.9 ± 15.5	97.8 ± 14.6	92.9 ± 14.2
ASA physical status (I/II)	30/12	31/11	30/12
Smoking (n)	6	4	8
History motion sickness and/or PONV (n)	17	14	15
Phase of menstrual cycle (n)			
Follicular	17	16	17
Luteal	18	20	15
Postmenopause	7	6	10

MABP, mean arterial blood pressure.
Data presented as mean ± SD or number of patients. Anesthesia was maintained with sevoflurane (Group S), propofol (Group P), or combined propofol and sevoflurane (Group PS).

rates (Group P) were titrated to achieve a target BIS value of 40–60. In Group PS, propofol infusion rate and sevoflurane concentration were fixed.

Intraoperative analgesia was performed by titrating remifentanil infusion at the discretion of the attending anesthesiologist. Neuromuscular blockade was maintained with intermittent rocuronium. Ringer's acetate solution was administered at 10 mL/kg/h for the first hour of anesthesia and at 5 mL/kg/h for all subsequent hours. Before the end of surgery, all patients received flurbiprofen axetil (1 mg/kg). At the end of surgery, neuromuscular blockade was reversed with atropine (0.5 mg) and neostigmine (1 mg).

The incidence and severity of PONV were assessed by blinded observers at 2 and 24 h after surgery. The severity of nausea was recorded using the following scale: no nausea, mild nausea, moderate nausea, and severe nausea. A complete response was defined as no PONV and no rescue antiemetic use. Intravenous metoclopramide (10 mg) was used as the rescue antiemetic. Postoperative pain was evaluated using a numerical rating scale (0 = no pain to 10 = maximal pain). When a patient requested analgesia, a diclofenac suppository (25 mg) or intramuscular pentazocine (15 mg) was administered. The 0–2 h and 2–24 h intervals were defined as early and late, respectively. The primary end point was the complete response rate within 24 h of surgery.

A previous study[10] reported a cumulative PONV incidence of 70% at 24 h in patients undergoing laparoscopic gynecological surgery. The sample size was determined by power analysis to provide a power of 0.8 to detect a 35% absolute decrease in the cumulative PONV incidence ($\alpha = 0.05$). Statistical analysis was performed with SPSS® version 18 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared by one-way analysis of variance, with Bonferroni *post hoc* tests for multiple comparisons. Categorical variables were analyzed using the χ^2 or Fisher's exact tests, with correction for multiple comparisons where appropriate. Data are expressed as number of patients or mean ± standard deviation. A p-value of <0.05 was considered statistically significant.

Results

Of 130 patients, four were excluded from this analysis: two who converted to laparotomy and two violated the study protocol. Therefore, 42 patients were randomly allocated to Group S, 42 to Group P, and 42 to Group PS.

Demographic data were similar with respect to age, weight, height, ASA physical status, smoking history, history of motion sickness and/or PONV, and menstrual cycle phase (Table 1). Similarly, there were no significant differences in intraoperative variables, including the duration of anesthesia and surgery, total doses of remifentanil and rocuronium, surgery type, temperature, blood loss, and intravascular fluid volume (Table 2).

A complete response at 24 h (primary end point) was achieved in 38% patients in Group S, 71% in Group P and 76% in Group PS ($p < 0.0005$) (Table 3). Groups P and PS differed significantly from Group S ($p = 0.012$ and < 0.002, respectively), but no significant difference was evident between Groups P and PS (Table 3). The incidence of nausea at 24 h was also significantly different (Group S = 62%, Group P = 29% and Group PS = 21%, $p < 0.0005$). The significant nausea rate was also lower in Group P and PS than in Group S ($p = 0.003$). However, there were no statistically significant differences among groups in the incidence or frequency of vomiting or rescue antiemetic use at 24 h (Table 3).

In the early postoperative period, the proportion of patients who experienced a complete response was significantly higher in Groups P (74%) and PS (76%) than in Group S (43%) ($p = 0.001$). The incidence of nausea was also significantly lower in Groups P (26%) and PS (21%) than in Group S (57%) ($p = 0.001$). However, there were no statistically significant differences among groups in the incidence or frequency of vomiting at this time (Table 3).

In the late postoperative period, although the incidence of nausea was lower in Groups P (12%) and PS (10%) than in Group S (26%), the difference was not statistically significant ($p = 0.078$). The proportion of patients exhibiting a complete response, the incidence and frequency of vomiting, severity of nausea, and rescue antiemetic use did not differ among groups during at this time (Table 3).

Table 2 Surgery/anesthesia-related parameters.

	Group S ($n=42$)	Group P ($n=42$)	Group PS ($n=42$)
Duration of anesthesia (min)	171.2 ± 58.6	167.9 ± 67.1	155.5 ± 48.7
Duration of surgery (min)	124.7 ± 54.5	122.1 ± 65.3	111.5 ± 48.7
Anesthetics			
Remifentanil (mg)	3.082 ± 1.884	3.197 ± 1.856	3.055 ± 1.420
Rocuronium (mg)	54.8 ± 13.2	53.1 ± 13.4	50.6 ± 13.0
Type of surgery (n)			
Ovarian cystectomy/tumorectomy	31	24	32
Adhesiolysis	2	5	2
Myomectomy	6	9	3
Salpingostomy	1	0	2
Ovarian drilling	1	0	1
Oophorectomy	1	4	2
Temperature (°C)	36.6 ± 0.4	36.4 ± 0.4	36.6 ± 0.6
Blood loss (mL)	28.8 ± 54.5	65.4 ± 142.7	31.4 ± 58.8
Fluid volume (mL)	1059.0 ± 312.3	1109.8 ± 440.9	1036.0 ± 341.1

Data presented as mean ± SD or number of patients.
Anesthesia was maintained with sevoflurane (Group S), propofol (Group P), or combined propofol and sevoflurane (Group PS).

Table 3 Incidence of postoperative nausea and vomiting.

	Group S ($n=42$)	Group P ($n=42$)	Group PS ($n=42$)	p-Value
0–2 postoperative hours				
Nausea	24 (57)	11 (26)[b]	9 (21)[b]	0.001[a]
Significant nausea (moderate or severe)	16 (38)	7 (17)	3 (7)[b]	0.001[a]
Vomiting	4 (10)	5 (12)	3 (7)	0.759
Vomiting episodes in patients who vomited	2.3 ± 1.5	1.2 ± 0.4	2 ± 1.7	0.155
Postoperative nausea and/or vomiting	24 (57)	11 (26)[b]	9 (21)[b]	0.001[a]
Rescue antiemetic	8 (19)	1 (2)	2 (5)	0.014[a]
Complete response	18 (43)	31 (74)[b]	33 (76)[b]	0.001[a]
2–24 postoperative hours				
Nausea	11 (26)	5 (12)	4 (10)	0.078
Significant nausea (moderate or severe)	1 (2)	3 (7)	2 (5)	0.592
Vomiting	2 (5)	4 (10)	2 (5)	0.586
Vomiting episodes in patients who vomited	1.5 ± 0.7	2.3 ± 1.5	3 ± 0	0.530
Postoperative nausea and/or vomiting	11 (26)	5 (12)	4 (10)	0.078
Rescue antiemetic	2 (5)	3 (7)	0 (0)	0.233
Complete response	31 (74)	36 (86)	38 (90)	0.108
0–24 postoperative hours				
Nausea	26 (62)	12 (29)[b]	9 (21)[b]	<0.0005[a]
Significant nausea (moderate or severe)	17 (40)	8 (19)	4 (10)[b]	0.003[a]
Vomiting	4 (10)	6 (14)	3 (7)	0.549
Vomiting episodes in patients who vomited	3 ± 2.2	2.5 ± 1.2	4 ± 3	0.651
Postoperative nausea and/or vomiting	26 (62)	12 (29)[b]	9 (21)[b]	<0.0005[a]
Rescue antiemetic	9 (21)	4 (10)	2 (5)	0.052
Complete response	16 (38)	30 (71)[b]	33 (76)[b]	<0.0005[a]

Data presented as mean ± SD or number of patients (%).
Anesthesia was maintained with sevoflurane (Group S), propofol (Group P), or combined propofol and sevoflurane (Group PS).
[a] Statistically significant difference ($p < 0.05$).
[b] Statistically significant difference from Group S ($p < 0.05$).

Table 4 Postoperative pain data.

	Group S ($n = 42$)	Group P ($n = 42$)	Group PS ($n = 42$)
Numerical rating scale (0–10)			
Postoperative at			
2 h	6.4 ± 2.5	5.6 ± 2.3	5.9 ± 3.0
24 h	4.1 ± 2.3	3.7 ± 1.9	3.8 ± 2.4
Postoperative diclofenac sodium (mg)	17.3 ± 18.7	16.7 ± 18.0	17.9 ± 18.5
Postoperative pentazocine (mg)	7.9 ± 8.9	8.6 ± 13.7	4.6 ± 7.4

Data presented as mean ± SD.
Anesthesia was maintained with sevoflurane (Group S), propofol (Group P), or combined propofol and sevoflurane (Group PS).

There was no difference among groups in the numerical rating scale or analgesia use (Table 4). No patients reported intraoperative awareness.

Discussion

This study demonstrates that the use of combined propofol and sevoflurane anesthesia during laparoscopic gynecological surgery decreases PONV incidence. This is the first study, as per our knowledge, to assess the effects of combined propofol and volatile anesthesia on PONV incidence.

The use of volatile anesthetics such as isoflurane and sevoflurane has many benefits. The representative beneficial effect is cardioprotection. Volatile anesthetics have been shown to protect the myocardium against myocardial ischemia and reperfusion injury through a signal transduction pathway that includes protein kinase C and mitochondrial and sarcolemmal KATP channels.[1,2] Reportedly,[3,4] volatile anesthetics also cause coronary vasodilatation by activating vascular KATP channels. Randomized clinical trials in patients undergoing coronary artery surgery have demonstrated that volatile anesthetics decrease troponin release, the duration of intensive care unit stay, and the incidence of late cardiac events and enhance left ventricular function.[11] On the basis of these trials, the American College of Cardiology/American Heart Association 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery[11] recommend the use of volatile anesthetic agents during noncardiac surgery for maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia (Class IIa, level of evidence B). The additional benefits of volatile anesthesia include a lower incidence of intraoperative awareness during general anesthesia[12] and a bronchodilatory effect.[13]

TIVA with propofol is associated with a lower PONV incidence.[5,6] In addition, TIVA has many advantages over volatile anesthesia. Several studies[7] have shown that propofol causes a dose-related decrease in cerebral blood flow, the rate of cerebral metabolism of oxygen, and intracranial pressure. Animal studies[14] have demonstrated that volatile anesthetics inhibit hypoxic pulmonary vasoconstriction (HPV) in a dose-dependent manner, although propofol does not seem to affect HPV.[15] Although it remains controversial whether propofol can induce malignant hyperthermia (MH),[16] Sumitani et al.[17] reported a relatively low prevalence of MH in propofol users. Previous studies[8] have demonstrated that patients anesthetized with propofol experience less pain than those anesthetized with volatile anesthetics. Furthermore, TIVA was shown to be more effective in inhibiting the neuroendocrine stress response compared with volatile anesthesia.[9] Propofol may also prevent tissue damage resulting from oxidative stress[18] through its antioxidant properties.[19]

Propofol and volatile anesthetics such as sevoflurane and desflurane are extensively used for clinical anesthesia because of the rapid onset and cessation of action. The use of each anesthetic has both advantages and disadvantages. We developed a novel method of anesthesia combining propofol and volatile anesthesia to receive the benefits and decrease the disadvantages of each anesthetic. However, this was just a hypothesis, and the actual effects of combination remain unknown. Therefore, we evaluated the effects of combined propofol and volatile anesthesia on PONV incidence in patients undergoing laparoscopic gynecological surgery.

The results of this study showed that the use of combined propofol and volatile anesthesia during laparoscopic gynecological surgery caused a 66% reduction in PONV (from 62% to 21%), an effect that was more pronounced in the early postoperative period. Surprisingly, this effect is comparable with that of TIVA with propofol (a 66% decrease in Group PS *versus* a 53% decrease in Group P). The PONV incidence in Group S (62%) was similar to the previously reported PONV incidence undergoing laparoscopic gynecological surgery.[10,20]

Patients in Group PS received significantly smaller doses of sevoflurane during anesthesia, which may explain the decreased PONV incidence. Apfel et al.[21] reported that the degree of exposure to volatile anesthetics is the primary cause of PONV in the early postoperative period. Another reason for the decreased PONV incidence could be the antiemetic effects of propofol. The antiemetic properties of propofol were first demonstrated by Borgeat et al.[22] and subsequently by several other authors.[23] However, its precise mechanism of action remains unclear. Propofol may act as a dopamine receptor antagonist.[24] It has also been shown to possess a weak antagonistic effect against serotonin. However, the precise mechanism by which propofol exerts its antiemetic effects remain undetermined. Reportedly,[25] the effect is associated with a defined plasma concentration range; the plasma propofol concentration associated with a 50% decrease in nausea scores was found to be 343 ng/mL. According to the pharmacokinetic simulation (TIVA trainer 8, Frank Engbers, Leiden, The Netherlands), 155 min after an induction dose of 1.5 mg/kg and maintenance with 2 mg/kg/h, the plasma concentration of propofol is 1 μg/mL.

Simulation data also demonstrate that the plasma propofol concentration drops below 350 ng/mL within approximately 170 min of the end of infusion. These simulation data suggest that the plasma concentration of propofol used in our method will above the range effective for antiemesis until approximately 170 min after the end of surgery. This probably explains why patients in Group PS exhibited a lower incidence of PONV, particularly in the early postoperative period.

Limitations of the study

Our study has some limitations. First, there is increasing consensus that better PONV prophylaxis can be achieved through the use of a combination of agents acting on different receptors, considering that multiple receptors are involved in the etiology of PONV. In high-risk patients, a multimodal approach to prevent PONV has been recommended. However, we did not administer any prophylactic antiemetic or combined agents to prevent PONV. This is because we wanted to investigate the baseline risk, which could have been masked by prophylactic antiemetic. Decreasing the baseline risk has been recommended[26] because it can significantly decrease PONV incidence.[27,28] In addition, prophylactic antiemetic are associated with an increase in both costs and adverse effects.[29,30] Therefore, we considered it important to study the pure incidence of PONV for each method of anesthesia. Second, only one combination of propofol infusion rate and sevoflurane concentration was studied, and the effects of other combinations were not assessed in this study. Therefore, the optimal combination of propofol infusion rate and sevoflurane concentration remains to be determined.

Conclusions

In conclusion, combined propofol and volatile anesthesia during laparoscopic gynecological surgery effectively decreases PONV incidence in the absence of prophylactic antiemetic. Although further experimental research is required to clarify its efficacy in a clinical context, we believe that combined propofol and volatile anesthesia offers potential clinical benefits. We term this novel method of anesthesia ''combined intravenous-volatile anesthesia (CIVA)''.

Conflicts of interest

The authors declare no conflicts of interest.

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