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ORIGINAL ARTICLE

Desflurane reinforces the efficacy of propofol target-controlled infusion in patients undergoing laparoscopic cholecystectomy

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Abstract Whether low-concentration desflurane reinforces propofol-based intravenous anesthesia on maintenance of anesthesia for patients undergoing laparoscopic cholecystectomy is to be determined. The aim of this study was to investigate whether propofol-based anesthesia adding low-concentration desflurane is feasible for laparoscopic cholecystectomy. Fifty-two patients undergoing laparoscopic cholecystectomy were enrolled in the prospective, randomized, clinical trial. Induction of anesthesia was achieved in all patients with fentanyl 2 μg/kg, lidocaine 1 mg/kg, propofol 2 mg/kg, and rocuronium 0.8 mg/kg to facilitate tracheal intubation and to initiate propofol target-controlled infusion (TCI) to effect site concentration (Ce: 4 μg/mL with infusion rate 400 mL/h). The patients were then allocated into either propofol TCI based (group P) or propofol TCI adding low-concentration desflurane (group PD) for maintenance of anesthesia. The peri-anesthesia hemodynamic responses to stimuli were measured. The perioperative psychomotor test included p-deletion test, minus calculation, orientation, and alert/sedation scales. Group PD showed stable hemodynamic responses at CO_2 inflation, initial 15 minutes of operation, and recovery from general anesthesia as compared with group P. There is no significant difference between the groups in operation time and anesthesia time, perioperative psychomotor functional tests, postoperative vomiting, and pain score. Based on our findings, the anesthetic technique combination propofol

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and desflurane for the maintenance of general anesthesia for laparoscopic cholecystectomy provided more stable hemodynamic responses than propofol alone. The combined regimen is recommended for patients undergoing laparoscopic cholecystectomy.

Introduction

Laparoscopic cholecystectomy (LC) provides patients less postoperative pain, more rapid mobilization, faster return to normal activities, and earlier hospital discharge as compared to traditional open cholecystectomy [1–3], and general anesthesia is the standardized anesthetic technique of choice for this procedure [4]. Desflurane has a lower blood:gas solubility coefficient (0.47) than other volatile anesthetics, and provides rapid induction and recovery from anesthesia [5,6]; however, desflurane easily leaks out to the air and blunts the protective responses in anesthetists and medical personnel who are exposed in the environment. Hence, LC surgery under total intravenous anesthesia (TIVA) was chosen as an alternate option. Propofol is a short-acting general anesthetic agent used widely for TIVA because of the beneficial effects on antiemetic properties and rapid recovery time [7,8]. For general anesthesia, opioids given for the alleviation of surgical-injury-induced pain also decrease the propofol dose or decrease the inhaled anesthetics concentration, but inevitably the decreased general anesthetics cannot ensure loss of consciousness and lack of awareness [9,10]. Propofol and desflurane are therefore suitable because of their recommended pharmacological properties [11,12]. However, propofol provides less potency, and the patient consumes more opioids to relieve pain as compared to desflurane [13]. Whether propofol target-controlled-infusion (TCI) combination of low-concentration desflurane provides a proper regimen for patients undergoing LC surgery is not yet determined. We hypothesize that the regimen of propofol TCI adding low-concentration (3%) desflurane might reinforce the anesthetic effect and provide better hemodynamic stability for LC. The study was designed to assess the feasibility of two propofol-based anesthetic regimens (desflurane with propofol vs. propofol alone) with fixed fentanyl continuous infusion to maintenance profile in patients undergoing LC.

Methods

The study was approved by the local Institutional Review Board (KMUK-IRB-990201). Fifty-two American Society of Anesthesiologists physical status I and II patients, aged 21–63 years, scheduled for elective LC, were enrolled in this prospective, randomized, clinical study after their written informed consents were obtained. The patients were randomly assigned to one of the following two anesthesia groups for maintenance during operation: propofol TCI and low-concentration desflurane (group PD), or propofol TCI alone (group P). The exclusion criteria were severe systemic disease, morbid obesity, and patient refusal.

According to the study protocol, standard monitoring was installed upon arrival in the anesthetic room. Oxygen was offered via an anesthetic breathing circuit and facemask. After 3-minute preoxygenation, the induction of anesthesia was achieved in all patients with fentanyl 2 μg/kg, lidocaine 1 mg/kg, propofol 2 mg/kg, and rocuronium 0.8 mg/kg to facilitate tracheal intubation and to initiate propofol TCI (Ce: 4 μg/mL, infusion rate 400 mL/h) using a TCI pump (EP-1809-1; Fresenius Kabi, Bad Homburg, Germany) to blunt intubation-induced hemodynamic responses and to maintain general anesthesia. For the maintenance of anesthesia, patients in group PD received propofol TCI with fentanyl (1 μg/kg/h) and desflurane at an end-tidal concentration of 3%. Patients in group P received propofol TCI (Ce: 4 μg/mL) with fentanyl (1 μg/kg/h). As compared with the baseline mean arterial pressure (MAP) value, if hemodynamic responses deviate up each 10% MAP values, increased propofol Ce level 0.5 and fentanyl 0.5 μg bolus; if hemodynamic responses deviate down 10% MAP values, decreased propofol Ce level 0.5 and administered ephedrine 8 mg intravenously as over 20% MAP dropped.

The primary outcome was measured by the hemodynamic stability. The parameters of hemodynamic response included heart rate and MAP; the response was measured by heart rate and MAP difference from baseline value. During anesthesia, hemodynamic responses to stimuli were measured at each time point of pre-intubation as baseline (PI), post-intubation (PoI), pre-CO_2 insufflation (PC), post-CO_2 insufflation (PoC), operation time every 5 minutes to 35 minutes (Op5 to Op35), remove trocar (Rt), set Ce level back to 2 (Ce2), stop propofol infusion (stop-P), spontaneous breathing (SB), and remove endotracheal tube (Rendo). Perioperative psychomotor tests that included a p-deletion test (a set time test in which patients identify the p's in lines of random letters), observer's assessment of alertness/sedation (OAA/S) scale (0–5), attention and calculation (0–5), and orientation (0–10) were performed at preoperation and 60 minutes after the end of surgery.

Following the end of surgery, postoperative pain, nausea and vomiting, and complication were also assessed by the unaware nurse assistant. All patients rated their postoperative pain using a 10-point numeric rating scale (from 0 = no pain to 10 = worst pain). All postoperative observations were completed by the same nurse anesthetist who was unaware to the study-grouping patients. Intravenous ketorolac 30 mg was the first-line rescue analgesia, and pethidine 50 mg was considered as the second rescue analgesics if needed. Postoperative nausea and vomiting (PONV) was treated with metoclopramide as needed. Resource utilization included anesthesia time, operation time, and consumption of anesthetic agents.

To determine of the sampling size was based on a study of hemodynamic responses to surgical intervention as patients undergoing LC with target-controlled propofol infusion. A mean difference of 11 MAP between groups with a standard deviation of 13 mmHg revealed at least a group size of $n = 23$ to detect a difference with a power of 0.8 at the α level of 0.05 [14]. Therefore, the study enrolled 26 patients in each group (110% of the minimum required patients). Data are presented as mean values and standard deviation. Differences and frequencies between groups were analyzed using the Student t test or Pearson χ^2 test as appropriate. A p value < 0.05 was considered statistically significant. The statistical analyses for the study were performed using SPSS 12.0 for Windows (SPSS Inc., 233 South Wacker Drive, 11th Floor Chicago, IL 60606-6412).

Results

Fifty patients were into final analysis, including 26 patients in group PD and 24 patients in group P. Two out of 26 patients in group P failed to allocate into analysis, one for unexpected difficult intubation and the other one for unintentional intravenous set leaks (Figure 1).

The MAP difference (each time-interval MAP value minus baseline MAP value) shown in Figure 2 presents more stable hemodynamic responses to various stimuli in group PD than the hemodynamic responses in group P. There are significant differences between groups at time intervals of PoC ($p < 0.05$), Op5 ($p < 0.01$), Op10 ($p < 0.01$), Op15 ($p < 0.05$), Ce2 ($p < 0.05$), and Stop-P ($p < 0.05$). As regards the heart-rate difference (each time interval minus baseline), it presents more stability of heart rate in group P than in group PD. There is a significant difference between groups at PoC time interval.

There are no significant differences in demographic characteristics, anesthetic time, operation time, and consumption of anesthetic agents between groups (Tables 1 and 2). In addition, there is no significant difference on perioperative psychomotor functional tests (Table 3), and requirement of postoperative analgesia, pain score, and incidence of PONV (Table 4) between groups.

Discussion

Previous studies focused on comparing propofol with inhalational agents; the advantages of propofol-based general

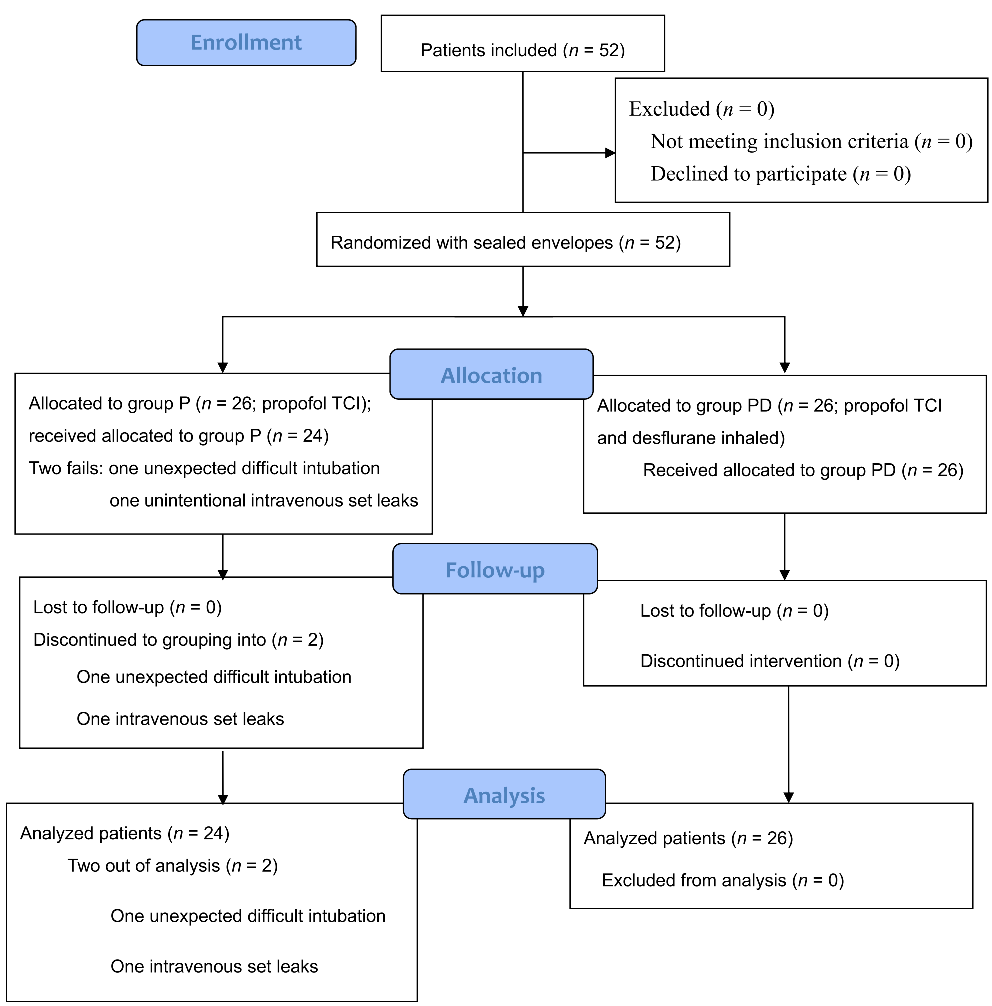

Figure 1. Flowcharts of patients undergoing laparoscopic cholecystectomy allocated either group PD or group P. TCI = target-controlled infusion.

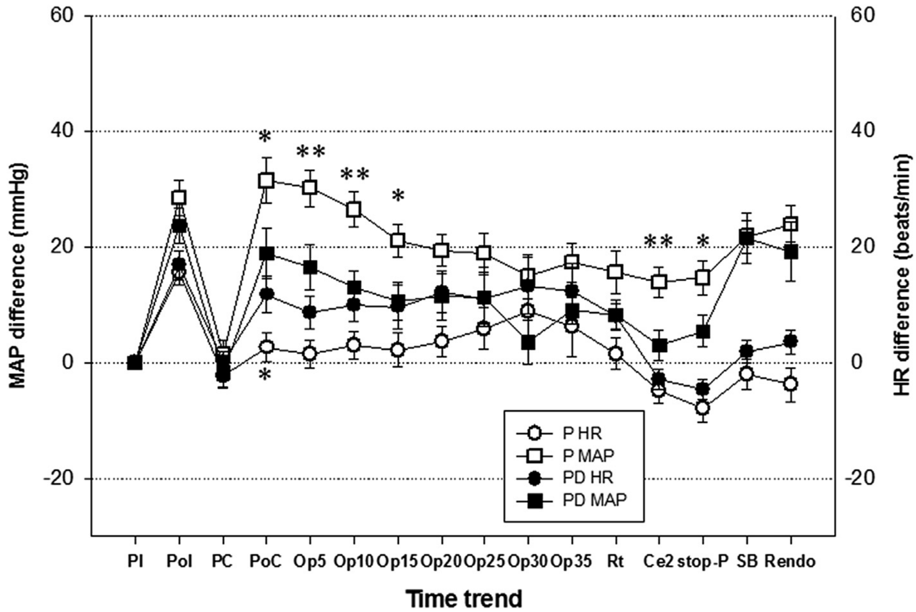

Figure 2. Hemodynamic responses to various stimuli during peri-anesthesia period. Group PD presents mean arterial pressure and heart rate more stable than group P at time intervals of PoC, Op5, Op10, Op15, Ce2, and stop-P, respectively. Ce2 = effect-site concentrations of propofol back to 2; HR = heart rate (beats/min); MAP = mean arterial pressure (mmHg); Op5 to Op35 = operation time every 5 minutes to 35 minutes; PC = pre-CO_2 insufflation; PI = pre-intubation as baseline; PoC = post-CO_2 insufflation; PoI = post-intubation; Rendo = remove endotracheal tube; Rt = remove trocar; SB = spontaneous breathing; stop-P = stop propofol target-controlled infusion.

anesthesia have become an alternative choice because of its rapid clearance and improvements in well-being [7,11,15]. In this study, the novel regimen still provides the advantages of propofol-based general anesthesia for LC patients, but limits use of opioid by instead using low-concentration desflurane. Due to the primary outcome measure of the hemodynamic stability between groups, opioid consumptions between groups did not show statistical difference. However, the authors believe that a larger sample size of group patients would present the statistical difference in propofol and opioid consumptions in group P as compared with the group PD. The study simply demonstrates that the regimen of propofol-based general anesthesia adding low-concentration desflurane, not only provides stable hemodynamics during the perioperative period, but also reduces opioid and propofol consumption.

The present study found that patients undergoing LC surgery with propofol-based general anesthesia adding low-concentration desflurane had less MAP change at stages of CO_2 inflation (reverse Trendelenburg position and pneumoperitoneum), within 15 minutes of initiation of operation (surgical stimuli), and recovery from general anesthesia (withdrawal of propofol). In our study, the propofol TCI with desflurane provided satisfactory anesthesia for LC and smooth recovery when compared with propofol TCI alone. With the addition of desflurane, a hemodynamic change in TCI with propofol was attenuated. It may be related to the vasodilation effect of desflurane, which resulted in dose-dependent reductions in systemic vascular resistance and arterial blood pressure [6]. Unlike MAP, the heart-rate

Table 1 Demographic data of the study population.

Variable	Group PD (n = 26)	Group P (n = 24)	p
Sex			0.216
Male	12 (46.2%)	7 (29.2%)	
Female	14 (53.8%)	17 (70.8%)	
Age (y)	44.15 (23–61)	47.13 (31–60)	0.295
Body mass index (kg/m^2)	25.55 (4.00)	24.29 (3.42)	0.240
ASA physical status (I/II)			0.954
Class I	1 (3.8%)	1 (4.2%)	
Class II	25 (96.2%)	23 (95.8%)	

Values are expressed as numbers (proportion), median (interquartile range), or mean (standard deviation) as appropriate. ASA = American Society of Anesthesiologists.

Table 2 Medical resource utilization.

	Group PD (n = 26)	Group P (n = 24)	p
Anesthesia time (min)	102.24 (30.03)	103.40 (32.27)	0.183
Operation time (min)	55.48 (25.41)	58.63 (26.48)	0.111
Fentanyl (μg)	125.17 (21.88)	138.11 (26.44)	0.070
Propofol (mg)	125.30 (21.75)	140.11 (29.76)	0.055
2% Xylocaine (mg)	62.65 (10.87)	69.09 (13.19)	0.071
Rocuronium (mg)	50.12 (8.70)	54.93 (10.46)	0.089

Values are expressed as mean (standard deviation).

Table 3 Comparison of psychomotor status.

	Group PD (n = 26)	Group P (n = 24)	p
P-deletion			0.205
Pre-op	44.6 ± 9.1	44.8 ± 7.5	
Post-op	37.8 ± 8.7	36.6 ± 15.1	
OAA/S (5/4/3)			0.264
Pre-op	26/0/0	24/0/0	
Post-op	21/4/1	18/6/0	
Orientation (10-9/8-6/0)			0.460
Pre-op	26/0/0	24/0/0	
Post-op	26/0/0	24/0/0	
Minus calculation (5/4-1/0)			0.316
Pre-op	26/0/0	24/0/0	
Post-op	24/1/1	19/4/1	

Postoperation: 60 minutes after the end of surgery.
OAA/S = observer's assessment of alertness/sedation scale; Post-op = post-operative; Pre-op = pre-operative.

difference between the two groups was not significant except in the stage of post-CO_2 inflation. However, the rate-pressure product presents a similar trend between groups. It validates that low-concentration desflurane added to the regimen of propofol-based anesthesia decreased the fentanyl and propofol dosages, but did not increase the hemodynamic responses to surgical stimuli.

PONV is an important issue of patient satisfaction and is a common phenomenon after laparoscopic procedures. Prior studies have shown that TIVA reduces PONV compared with volatile anesthesia [16—23]; however, there was no significant difference between the two groups in our study. The study results also showed that, when propofol TCI was used as mainstay of anesthetic technique either with or without desflurane, the PONV incidence was low. This might be explained by the antiemetic effect of propofol only required as low as 20—30 mg. Furthermore, low incidence with propofol TCI was presented during the whole course after operation. Nevertheless, the postoperative pain and psychomotor status are similar.

Table 4 Requirement of postoperative analgesia, pain score, and incidence of postoperative nausea and vomiting.

	Group PD (n = 26)	Group P (n = 24)	p
Post-op analgesia			0.935
Ketorolac	15 (57.7%)	17 (70.8%)	
Ketorolac + pethidine	11 (42.3%)	7 (29.2%)	
VAS			0.262
Score 1—3	10 (38.5%)	13 (54.2%)	
Score 4—6	15 (57.7%)	11 (45.8%)	
Score 7—10	1 (3.8%)	0 (0.0%)	
PONV			0.954
None	25 (96.2%)	23 (95.8%)	
Mild	1 (3.8%)	1 (4.2%)	

Postoperation: 60 minutes after the end of surgery. Values are expressed as numbers (proportion).
PONV = postoperative nausea and vomiting; Post-op = post-operative; VAS = visual analogue scale.

There are several limitations in this study. First, since desflurane was delivered via a vaporizer, a double-blind strategy was unable to be performed in the study. Second, we used fentanyl with propofol TCI instead of remifentanil for the reason that we do not have remifentanil in our hospital. Remifentanil is a μ-opioid receptor agonist with a quick onset and peak effect, as well as a short duration of postoperative activity, and may be a better agent for short-duration surgery. Third, the conscious-level monitor, such as entropy or bispectral index, was not available during the study period, but instead of maintaining stable hemodynamia during operation. Although we could not prove the same anesthetic depth in both groups, those patients recovered without explicit memory. In addition, regular anesthetic care was delivered by a single experienced nurse anesthetist to ensure the standardized anesthesia protocol.

In conclusion, propofol TCI with low-concentration desflurane for anesthesia maintenance provided more stable hemodynamic responses than propofol TCI alone. The novel regimen did not diminish the advantage of propofol TCI with low PONV incidence, but had a trend to save propofol and opioid dose. Therefore, we recommend that the regimen is practicable to patients undergoing LC.

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