Retrospective Comparison between the Effects of Propofol and Inhalation Anesthetics on Postoperative Recurrence of Early- and Intermediate-Stage Hepatocellular Carcinoma

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Significance of the Study

- Propofol and inhalation anesthetics can differently influence postoperative recurrence of hepatocellular carcinoma (HCC) in a clinical setting.
- Postoperative 2-year HCC recurrence was decreased when propofol was used as the main anesthetic.
- Propofol should be considered as optimal anesthetic for patients with early-stage HCC undergoing hepatic resection.

Keywords

Anesthesia · Hepatic resection · Hepatocellular carcinoma · Inhalation anesthetic · Propofol · Tumor progression

Abstract

Objective: Previous studies have reported that propofol has antitumor, anti-inflammatory, and antioxidant effects in addition to its anesthetic properties. To confirm this, a retrospective investigation was conducted to determine whether different anesthetic agents, particularly propofol and inhalation anesthetics, have an effect on the recurrence of hepatocellular carcinoma (HCC) in patients who were diagnosed with primary HCC and underwent laparoscopic hepatectomy. **Subjects and Methods:** Patients with Barcelona Clinic Liver Cancer stages 0, A, and B HCC, who underwent laparoscopic hepatic resection, were enrolled in this study. Postoperative HCC recurrence, which was determined from post-

operative liver CT, was evaluated 24 months postoperatively with respect to the main anesthetic agents. The characteristics of HCC and other patient-related or surgery-related variables were evaluated together. **Results and Conclusion:** During the 24-month period after hepatic resection, less HCC patients in the propofol group than in the inhalation group recurred ($p = 0.046$). The mean time to recurrence was 20.8 months (95% CI, 19.7–22.0) and 19.1 months (95% CI, 17.8–20.4) in the propofol group and the inhalation group, respectively. In addition, multivariable Cox proportional regression analysis revealed that the propofol group showed significantly decreased recurrence versus the inhalation group (hazard ratio, 0.57; 95% CI, 0.47–0.69; $p = 0.029$). When propofol was used as the main general anesthetic agent for laparoscopic hepatic resection, the postoperative 2-year recurrence rate decreased in early- and intermediate-stage HCC.

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Introduction

Hepatocellular carcinoma (HCC) is a solid type of cancer that has high recurrence and mortality rates [1]. Although locoregional treatments such as radiofrequency tumor ablation (RFA) and transarterial chemoembolization (TACE) can be applied, surgical resection or liver transplantation is the ultimate curative option for patients with early-stage HCC [1, 2]. Nevertheless, postoperative HCC recurrence has previously been determined to be about 50% in 2 years [3, 4], and several characteristics of HCC, such as tumor differentiation, tumor size and number, and vascular invasion, are risk factors for recurrence [3, 5]. In addition, nuclear factor (NF)- κ B, natural killer (NK) cells, and several interleukins (IL) have been reported to be linked with the progression or recurrence of HCC [6, 7].

Propofol and inhalation anesthetics, which are widely used anesthetics, function quite differently. Inhalation anesthetics decrease the activity of NK cells, while propofol does not suppress NK cell activity [8]. Moreover, propofol reduces the level of NF- κ B, tumor necrosis factor (TNF)- α , IL-1 β , and IL-6, thus providing antioxidant and anti-inflammatory effects [9, 10]. Additionally, propofol has been shown to inhibit the migration and invasion of human cancer cells [11, 12]. Previous studies reported better outcome in HCC patients when propofol was used for sedation or general anesthesia [13, 14].

In this study, patients with early- or intermediate-stage HCC were enrolled, and a retrospective investigation was performed to evaluate the difference in the recurrence rate after hepatectomy for HCC according to the main anesthetic agents used, propofol or inhalation anesthetic.

Subjects and Methods

Study Population and Data Collection

This study was approved by the local Institutional Review Board of the Seoul National University Bundang Hospital. The requirement for written informed consents was waived. The cohorts included comprised patients who were diagnosed with primary HCC and underwent elective laparoscopic hepatic resection between April 2003 and June 2013. The Barcelona Clinic Liver Cancer (BCLC) staging classification was limited to 0, A, and B.

General Anesthesia

General anesthesia was usually performed in the following manner. Midazolam was given to the patients commonly at the preoperative holding area. General anesthesia was induced under routine monitoring, which included electrocardiogram, invasive arterial pressure measurement, and pulse oximetry. Three anesthesiologists had chosen an inhalation anesthetic, and the other 2 anesthesiologists had performed total intravenous anesthesia during anesthesia maintenance for laparoscopic hepatic resection. When the inhalation anesthetic was chosen as the main anesthetic, propofol, rocuronium, and remifentanyl were given only for initial sedation, neuromuscular block, and pain control, respectively. When total intravenous anesthesia was planned, propofol and remifentanyl were administered via the target-controlled infusion method, and rocuronium was given intermittently.

Assessment of Postoperative HCC Recurrence

Postoperative HCC recurrence was evaluated for 24 months postoperatively. Postoperative serial liver computed tomography (CT) was evaluated to judge the recurrence of HCC at intervals of 3–6 months. All liver CT scans were finally evaluated by certified radiologists. When HCC recurrence was visualized on liver CT, the time to recurrence after hepatic resection was recorded together.

Other Outcome Variables

Various factors that could influence the recurrence of HCC were evaluated as follows: (1) Child-Pugh score and BCLC staging classification; (2) preoperative laboratory results; (3) preoperative

Fig. 1. Flow diagram of patient enrollment. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

Table 1. Characteristics of the patients, surgery, and hepatocellular carcinoma

	Propofol (<i>n</i> = 121)	Inhalation anesthetic (<i>n</i> = 138)	<i>p</i> value
<i>Patient characteristics</i>			
Age, years	61.4±10.3	64.5±11.4	0.155
Gender, males/females	94/27 (77.7/22.3)	106/32 (76.8/23.2)	0.985
Height, cm	166.4±7.9	163.4±7.8	0.048
Weight, kg	66.5±9.6	63.3±10.2	0.108
Child-Pugh A/B	111/10 (91.7/8.3)	130/8 (94.2/5.8)	0.593
BCLC 0/A/B	29/69/23 (24.0/57.0/19.0)	30/88/20 (21.7/63.8/14.5)	0.737
<i>Preoperative laboratory findings</i>			
HBsAg+	81 (66.9)	99 (71.7)	0.483
Anti-HCV+	13 (10.7)	10 (7.2)	0.442
α-Fetoprotein, ng mL ⁻¹	201.6±599.7	210.7±615.1	0.939
PIVKA-II, mAU mL ⁻¹	33.0±34.8	50.2±50.9	0.246
ICG test	9.3±8.1	11.1±10.0	0.394
Hb, g dL ⁻¹	14.2±1.5	13.9±1.7	0.264
Platelets, ×10 ³ μL ⁻¹	152±47	144±59	0.468
PT INR	1.06±0.09	1.10±0.12	0.060
aPTT, s	36.8±3.9	37.3±3.5	0.489
AST, IU L ⁻¹	32.9±19.5	39.5±25.9	0.166
ALT, IU L ⁻¹	34.1±27.2	41.7±49.5	0.381
ALP, IU L ⁻¹	81.4±24.8	84.8±34.1	0.590
γ-GT, IU L ⁻¹	63.9±85.5	61.1±54.1	0.830
Total bilirubin, mg dL ⁻¹	0.9±0.3	0.8±0.5	0.852
Albumin, g dL ⁻¹	4.2±0.4	4.1±0.4	0.109
Creatinine, mg dL ⁻¹	0.9±0.3	1.0±0.9	0.447
Glucose, mg dL ⁻¹	109.0±29.3	114.1±48.4	0.551
<i>Surgical findings</i>			
Operation time, min	315.3±167.2	275.4±151.9	0.190
Operator A/B/C/D	92/23/6/0 (76.0/19.0/5.0/0.0)	105/16/14/3 (76.1/11.6/10.1/2.2)	0.085
Surgical procedure			0.496
Tumorectomy/wedge resection	37 (30.6)	39 (28.3)	
Subsegmentectomy	7 (5.8)	8 (5.8)	
Segmentectomy	20 (16.5)	31 (22.5)	
Sectionectomy	47 (38.8)	43 (31.2)	
Hemihepatectomy	10 (8.3)	17 (12.3)	
Perioperative transfusion	23 (19.0)	30 (21.7)	0.697
<i>Pathologic findings and tumor staging</i>			
Solitary/multifocal HCC	111/10 (91.7/8.3)	130/8 (94.2/5.8)	0.593
HCC size (≥5 cm)	7 (5.8)	12 (8.7)	0.511
Grade of differentiation I/II/III	3/30/88 (2.5/24.8/72.7)	3/46/78 (2.4/36.2/61.4)	0.147
Capsular infiltration	37 (30.6)	40 (31.5)	0.985
BD invasion	3 (2.5)	0 (0.0)	0.201
Microvascular invasion	34 (28.1)	43 (33.9)	0.400
HCC TNM stage 1/2/3A	81/33/7 (66.9/27.3/5.8)	86/40/12 (62.3/29.0/8.7)	0.519
Cirrhosis of nontumorous liver	61 (50.4)	70 (51.7)	0.941
Minimal resection margin, mm	12.3±9.6	16.3±15.2	0.075

Data are presented as means ± SD or numbers (%). BCLC, Barcelona Clinic Liver Cancer; HBsAg, surface antigen of hepatitis B virus; anti-HCV, anti-hepatitis C virus antibody; PIVKA-II, protein induced by vitamin K absence/antagonist II; ICG, indocyanine green; PT INR, international normalized ratio of prothrombin time; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; HCC, hepatocellular carcinoma; BD, bile duct; TNM stage, tumor-node-metastasis stage. Data are missing for the following variables: γ-GT (9 cases), PIVKA-II (80 cases), α-fetoprotein (4 cases), ICG test (30 cases), grade of differentiation, capsular infiltration, and microvascular invasion (11 cases, respectively).

Fig. 2. Recurrence-free survival after hepatic resection for HCC. +, censored data in each group.

RFA or TACE; (4) surgical procedure, operator, and operation time; (5) pathologic findings of HCC; (6) main anesthetic agent and anesthesia time; and (7) perioperative transfusion.

Statistical Analysis

Continuous or categorical variables were expressed as the mean $\pm$ SD or number (proportion). Normality test was performed for continuous data using a Shapiro-Wilk test. Student's *t* test or χ^2 test was used where appropriate. The progression-free survival (PFS) was calculated and analyzed with the Kaplan-Meier survival analysis with log-rank test. Univariate Cox proportional regression analysis was performed to determine individual relationships among all covariates. Then the covariates with $p < 0.2$ were selected to form the univariate Cox proportional regression model and analyzed via multivariate Cox proportional regression model. The results of the Cox proportional regression analyses were presented as hazard ratios with 95% confidence interval (CI). IBM® SPSS® statistics version 22.0 (IBM Corporation, NY, USA) was used for all analyses and $p \leq 0.05$ was considered statistically significant.

Results

The following cases were excluded: patients who had HCC recurrence or metastasis to other organs when undergoing the operation, diagnosis other than HCC on the postoperative pathology, and intraoperative conversion from laparoscopic procedure to laparotomy. Finally, 259 patients were enrolled in this study for the analysis; 121 patients received propofol (propofol group) and 138 received inhalation anesthetic (inhalation group) (Fig. 1). The characteristics of the patients, surgery, and HCC are shown in Table 1.

The Kaplan-Meier curve of 24-month PFS according to the main anesthetic is shown in Figure 2. HCC recurred less in the propofol group than in the inhalation group ($p = 0.046$), and the mean time to recurrence was 20.8 months (95% CI, 19.7–22.0) and 19.1 months (95% CI, 17.8–20.4) in the propofol and the inhalation group, respectively.

The overall 24-month PFS rates after surgery were 77.7 and 65.2% in the propofol and the inhalation group, respectively ($p = 0.038$). The HCC recurrence according to the main anesthetic agent and other variables was compared separately in a univariate and subsequently in a multivariate Cox proportional regression model. The propofol group showed significantly lower recurrence rates than the inhalation group (hazard ratio, 0.66; 95% CI, 0.42–1.05; $p = 0.016$). The multivariate Cox proportional regression model also presented results similar to those exhibited by the propofol group, which significantly decreased recurrence rates (hazard ratio, 0.57; 95% CI, 0.47–0.69; $p = 0.029$) compared with the inhalation group (Table 2). In addition, other variables that significantly increased the 24-month recurrence rate were microvascular invasion and higher TNM stage in the multivariate Cox proportional regression model.

Discussion

This retrospective study showed that HCC patients with BCLC stage 0, A, or B had less postoperative recurrence when propofol was used as the main anesthetic agent compared to the use of inhalation anesthetic.

HCC is an inflammation-related cancer, and several risk factors for recurrence after surgical resection have been established: larger tumor size, multinodularity, worse differentiation, microvascular invasion, liver disease stage, age, and sex [3, 5]. In addition to these well-known pathological risk factors, it has recently been revealed that several molecular pathways with mediators such as IL-6, NF- κ B, NK cells, TNF- α , and signal transducer and activator of transcription 3 are related to hepatocyte regeneration and development of HCC [6, 7].

Previous studies have reported results similar to those of the present study. When propofol was used for sedation or general anesthesia, better survival was observed in HCC patients [13, 14]. In the present study, only patients with primary HCC of BCLC stage 0, A, or B were enrolled, and the surgical procedure was limited to laparoscopic hepatic resection in order to recruit early- or intermediate-stage HCC, limit the basal characteristics to specific

Table 2. Cox proportional regression analysis for progression-free survival

Variables	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Anesthesia, inhalation (ref.: inhalation)	0.66 (0.42–1.05)	0.016	0.57 (0.47–0.69)	0.029
Age	1.01 (0.98–1.03)	0.486		
Female (ref.: male)	0.46 (0.46–0.20)	0.070	0.21 (0.03–1.60)	0.133
BCLC stage (ref.: 0)				
A	1.19 (0.59–2.40)	0.633		
B	1.25 (0.51–3.09)	0.622		
HbsAg (ref.: negative)	1.03 (0.56–1.89)	0.938		
Anti-HCV (ref.: negative)	1.19 (0.43–3.29)	0.742		
α-Fetoprotein	1.26 (0.38–4.17)	0.004	1.00 (0.99–1.01)	0.129
PIVKA-II	1.58 (0.46–5.44)	0.002	1.05 (0.40–2.72)	0.330
ICG test	1.00 (1.00–1.01)	0.323		
Operation time	1.00 (1.00–1.00)	0.291		
Transfusion (ref.: no)	1.22 (0.66–2.23)	0.524		
Tumor number (ref.: single)	1.75 (0.75–4.08)	0.197	1.76 (0.30–3.12)	0.945
HCC size	1.99 (1.00–3.95)	0.049	1.96 (0.57–5.39)	0.323
Grade of differentiation (ref.: I)				
II	0.65 (0.09–4.77)	0.670		
III	0.70 (0.08–6.25)	0.748		
Capsular infiltration (ref.: no)	0.82 (0.45–1.49)	0.507		
BD invasion	2.38 (0.33–17.26)	0.391		
Microvascular invasion (ref.: no)	1.21 (1.06–1.74)	0.028	1.53 (0.89–2.64)	0.015
TNM stage (ref.: 1)				
2	1.85 (1.02–3.38)	0.044	1.58 (0.46–5.44)	0.001
3A	6.44 (2.98–13.89)	<0.001	7.34 (1.99–27.13)	0.006
Cirrhosis of nontumorous liver	1.24 (0.72–2.13)	0.434		
Minimal resection margin	1.76 (0.57–5.39)	0.323		

conditions, and reduce confounding factors as much as possible. As such, the characteristics and risk factors of HCC as described above seem to be comparable between both groups. Accordingly, other important risk factors for HCC recurrence such as macrovascular invasion to the hepatic artery, hepatic vein, or portal vein [3, 5] were not observed in any patient. Moreover, all laparoscopic hepatic resections resulted in R0 resection, and no patient underwent postoperative adjuvant therapy in this study population. Our results may provide further reinforcing evidence regarding the nonanesthetic advantage of propofol in early- or intermediate-stage HCC patients.

Previous studies have reported that propofol has anti-tumor, anti-inflammatory, and antioxidant effects in addition to its anesthetic properties [15]. On the contrary, inhalation anesthetics were reported to have immunosuppressive effects, although this remains a controversial issue [16].

Propofol has been reported to decrease the viability, proliferation, and invasion of HCC cells in vitro by controlling some microribonucleic acids [17, 18]. The num-

ber and proportion of NK cells have been shown to decrease and its function impaired in HCC patients [19]; NK cell suppression increases the susceptibility of tumor progression [20]. While inhalation anesthetics decreased NK cell function, propofol did not inhibit NK cell activity, contributing to upregulation of interferon- γ and reduce tumor cell retention or metastasis [8, 21]. NF- κ B is involved intricately in the progression of HCC as well as other kinds of cancers [22]. NF- κ B activation is observed in HBV- or HCV-infected livers and advanced liver diseases [23]. Promotion of HCC development was also observed by NF- κ B activation in *Mdr2*-knockout mice [24]. Propofol is known to downregulate NF- κ B [9, 10], but inhalation anesthetics have been reported to increase the nuclear level and transcription activity of NF- κ B [25]. The TNF inflammatory pathway is also involved in liver carcinogenesis, judging from the reduced tumorigenesis in TNF receptor type 1-knockout mice [26]. IL-6-knockout mice presented less hepatocarcinogenesis [27], which corresponded with the elevated IL-6 levels in HCC patients [28]. Therapeutic propofol levels have been shown

to reduce the biosynthesis of several proinflammatory cytokines, such as TNF- α , IL-6, and IL-1 β in activated macrophages [10]. However, each inhalation anesthetic agent seems to have varied complex effects on pro- or anti-inflammatory cytokines [16]. Besides, hypoxia-inducible factor-1 α (HIF)-1 α has been known to be correlated with tumor development and expressed in various kinds of human tumor cells [29], and propofol, unlike the inhalation anesthetic, inhibited HIF-1 α activation [30]. These anti-tumor, anti-inflammatory, and antioxidant effects of propofol on the HCC-related molecular pathway and several mediators may explain the low postoperative recurrence rate of HCC in this study.

A major limitation of this study is that the duration of observation for HCC recurrence was limited to 2 years postoperatively; hence, we were unable to verify the long-term prognosis. However, it has previously been established that early recurrence of HCC has mostly occurred within 1–2 years of resection [4]. An-

other study with a larger group of patients, including cases with higher BCLC stages, showed similar results at long-term follow-up [14]. Second, the recurrence of HCC was evaluated only by CT in the present study. However, other examinations, such as positron emission tomography-CT or magnetic resonance imaging, could be used to detect postoperative HCC recurrence [5].

Conclusions

Postoperative 2-year recurrence of early- and intermediate-stage HCC decreased when propofol was used as the main anesthetic during general anesthesia for laparoscopic hepatic resection. Propofol needs to be reconsidered as an optimal anesthetic for early- and intermediate-stage HCC patients undergoing hepatic resection surgery.

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