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# Comparing Intraoperative End-Tidal Sevoflurane Concentration in Cirrhosis to Non-cirrhosis Patients Undergoing Open Hepatic Resection

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## Abstract

**Background**: The effect of hepatic cirrhosis on anesthetic requirement is still uncertain. Some studies showed that, end stage hepatic disease or cirrhotic patients might have less inhalational anesthetic requirement than patients with normal hepatic function. In this study, during major hepatic resection, end-tidal sevoflurane concentration was compared between cirrhosis and non-cirrhosis patients.

**Methods**: Our prospective observational study included 30 patients with hepatic tumors undergoing open major hepatic resection. The patients were divided into two groups: cirrhosis group (n=15) and non-cirrhosis group (n=15). Thoracic epidural combined with general anesthesia was performed. End tidal sevoflurane concentration was adjusted with target BIS between 40-55. Morphine and lidocaine were given via epidural catheter for pain control during perioperative periods. The primary outcome of the study is mean end-tidal sevoflurane. Demographic data including age, sex, weight, ASA physical status and other secondary outcomes were obtained from anesthetic records.

**Results**: The mean end-tidal sevoflurane concentration was 1.59±0.23 vol.% in cirrhosis group and 1.67±0.19 vol.% in non-cirrhosis group (*P*=0.329). Minimal alveolar concentration (MAC) in cirrhosis group and non-cirrhosis group were 0.84±0.10 and 0.87±0.07 (*P*=0.330), respectively. There is no significant difference in demographic data except for the ASA status (*P*=0.002) and the duration of operation (*P*=0.033).

**Conclusion**: Our study shows that there is no difference in end-tidal sevoflurane concentration, minimal alveolar concentration between cirrhosis and non-cirrhosis.

**Keywords**: bispectral index, cirrhosis, hepatectomy, hepatocellular carcinoma, inhalation anesthesia, sevoflurane

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## Introduction

Cirrhosis is the risk factor for development of hepatocellular carcinoma (HCC), which is present in 70-90% of those who have primary hepatic cancer.[1] Recent advances in surgical techniques and postoperative care have made liver resection safe even in patients with higher-degree cirrhotic with portal hypertension.[2] However, liver cirrhosis has still become one of the major causes of morbidity and mortality. The mortality rates of cirrhotic patients undergoing abdominal surgery could be as high as 10%, 30% and 82% with Child-Turcotte-Pugh classes A, B and C, respectively.[3]

Preclinical and clinical data suggested that the severity of hepatic disease may have an effect on anesthetic requirements. A previous study has found that the minimal alveolar concentration (MAC) of sevoflurane in end stage hepatic disease or in cirrhotic patients was lower than that of patients with normal hepatic function.[4] The mechanisms of this decreased inhalational anesthetic requirement in cirrhotic patients are poorly understood, but there is some theoretical background that might explain this result. Since exogenous narcotics are known to reduce the MAC of sevoflurane[5], endogenous narcotics may have a similar effect. The level of Met-enkephalin, an endogenous opioid, was found to be higher in cirrhosis[6], thus cirrhotic patients may possibly demand a smaller dose of inhalational anesthetic than patients with normal hepatic function. Another hypothesis is that due to a diminished capability of the cirrhotic liver to metabolize inhalation agents, the requirement of sevoflurane may decrease.[7] The last hypothesis refers to association between hepatic cirrhosis and mild hepatic encephalopathy (MHE). MHE is highly prevalent in cirrhotic patients and can be seen between 30-84%.[8] Patients with MHE do not show evident neurological deficits but instead have discernible cognitive dysfunction. These changes in the brain might explain the decreased requirement of sevoflurane.[9]

Over usage of an inhalation anesthetic agents is associated with hypotension, delayed emergence and post-operative cognitive dysfunction.[10] This excessive use can increase morbidity and mortality in cirrhotic patients after abdominal surgery. Thus, appropriate and careful use of volatile anesthetic agents may reduce not only the volume of volatile consumption, but also cost and post-operative complications.

The aim of this study is to define the effect of hepatic cirrhosis on anesthetic requirement. Primary outcome of this prospective observational study was to compare the end-tidal concentration of sevoflurane in cirrhosis to non-cirrhosis patients. Secondary outcomes were MAC and total sevoflurane consumption (mL/h).

## Patients and methods

The study was conducted in accordance with the Declaration of Helsinki (World Medical Association 2013), using procedures approved by the Institutional Review Board (number 239/60) and was nationally registered (Thai Clinical Trials Registry; TCTR-20170929002). All patients undergoing major hepatic resection, defined as resection of 3 or more segments, between October 1, 2017-October 31, 2018 were recruited into this study. The following conditions were considered exclusion criteria: patients with known neurologic or psychiatric disorders, history of chronic sedatives usage and alcohol consumption,

clinically significant cardiovascular, respiratory or renal diseases, family history of malignant hyperthermia and body mass index (BMI) ≥30 kg/m$^2$.

Written informed consent for the study was obtained from the included patients. The patients were divided into two groups according to their clinical features and liver imaging findings as well as biochemical results, namely group C (cirrhosis group, n=15) and group N (non-cirrhosis group, n=15). Patients did not receive any sedative or analgesic premedication before induction of anesthesia, as recommended in the enhanced recovery after surgery protocol for liver surgery.[11] Combined mid-thoracic epidural (T7-T10) and general anesthesia were performed in all patients. Monitoring devices were comprised of continuous electrocardiography, pulse oximetry, non-invasive blood pressure, capnography. Surface electrodes for the BIS (BIS VISTA™, Aspect Medical system) were placed to the patient's forehead. After the induction of anesthesia double lumen catheter was inserted in the right internal jugular vein for central venous pressure measurement and a radial artery cannula was inserted for arterial pressure measurement and arterial blood gas test. A forced-air warming was used in both groups to maintain normothermia and the urine output was monitored. Morphine 0.07 mg/kg was administered via epidural catheter after intubation for pain control during perioperative periods. 1% lidocaine 3-5 ml were given via epidural catheter before surgical incision. Anesthesia was maintained with sevoflurane in $O_2$/air, ($FiO_2$ 50% with a fresh gas flow of 2 L/min). The end-tidal concentration of sevoflurane and MAC were adjusted to maintain BIS index of between 40 and 55. These two parameters were monitored from anesthetic machine and recorded every 5 minutes as other standards of monitoring. The ventilated tidal volume was set to 6 to 8 mL/kg to maintain normocapnia ($ETCO_2$, 35-40 mm Hg). Cisatracurium 1-2 mcg/kg/min was continuously infused intravenously.

Mean arterial pressure (MAP) was kept at a target of 65-75 mmHg depending on underlying medical conditions. Hypertension was defined as 20% increase of MAP from baseline while BIS was within a target range (40-55). Hypertension High blood pressure was treated with antihypertensive medication. If there was a surgical stimuli response that could not be suppressed by epidural analgesia, patient would be given intravenous fentanyl. Hypotension was defined as decrease of MAP from baseline while BIS was within a target range (40-55). Hypotension was treated by increasing the rate of fluid or administration of vasopressor medication according to clinical need. After completion of hepatic parenchymal dissection bleeding was replaced by blood product, colloid or crystalloid fluid. At the end of surgery, total volume of sevoflurane usage was recorded.

## Statistical analyses

The sample size was calculated by using the test for comparing two independent means. According to a previous study, mean end tidal sevoflurane levels in both non-cirrhotic and cirrhosis patients were 1.51±0.16 vol.% vs. 1.33±0.14 vol.% respectively.[9] We considered a 0.2 minimum clinical difference would be clinically significant. Therefore, we determined that a sample size of 11 patients per group would provide 80% significance and 95% confidence level. With an expected 20% drop out rate, the total number was 15 patients per group.

Continuous variables between the groups

were compared using the unpaired t test or Mann-Whitney U test and categorical variables were analyzed using the Fisher's exact test. All variables were tested for normality using the Shapiro-Wilk test. The data were presented as the mean±standard deviation or median [interquartile range], according to the normality of data distribution, or as a number (proportion). Statistical analysis was conducted using SPSS for Windows Version 22.0 (SPSS Inc., Chicago, IL, United States). An effect was considered statistically significant at $P < 0.05$.

## Results

The demographic data of the patients are shown in Table 1. Compared with those of non-cirrhotic patients, the ASA physical status was significantly higher, and the operative time was significantly lower in cirrhosis group. There were no other significant differences. Most patients in the cirrhosis group were diagnosed by regular surveillance due to chronic viral hepatitis or incidental imaging analysis. Using Child-Turcotte-Pugh scoring system, all of them were classified as Child class A. Since cirrhosis is an essential risk factor for the development of HCC, 14 out of 15 patients in cirrhosis group were diagnosed with HCC. In non-cirrhosis group, the pathology mostly came from secondary hepatic cancer[12] which was colorectal liver metastasis.

The results of end-tidal sevoflurane are presented in Figure 1. The mean of end-tidal sevoflurane concentration in patients with cirrhotic livers (group C) was 1.59±0.23 vol.% and that of non-cirrhotic livers (group N) was 1.67±0.19 vol.%. The difference between Groups C and N were not statistically significant ($P>0.05$). The mean MAC of sevoflurane was also not statistically significant (0.84±0.10 vs 0.87±0.07, $P=0.329$). The mean of total sevoflurane consumption, which was calculated by total volume of sevoflurane usage divided by operative hours, was significantly lower in patients with non-cirrhosis group compared to that of cirrhosis group (11.03±1.89 mL/h vs 13.64±2.10 mL/h, $P=0.001$*) as reported in Table 2.

## Discussion

BIS is one of several methods used to monitor depth of anesthesia. In this study we titrated the sevoflurane administration during major hepatic resection in cirrhotic and non-cirrhotic patients, to achieve BIS range of 40-55 which is a usual target to prevent awareness during general anesthesia. Our findings indicated that there was no significant difference of the end-tidal sevoflurane concentration between two groups. This observation is inconsistent with other published data.

In an animal model, the study demonstrated that the MAC of sevoflurane decreased significantly in rabbits with chemically induced liver fibrosis compared to the control group.[13]

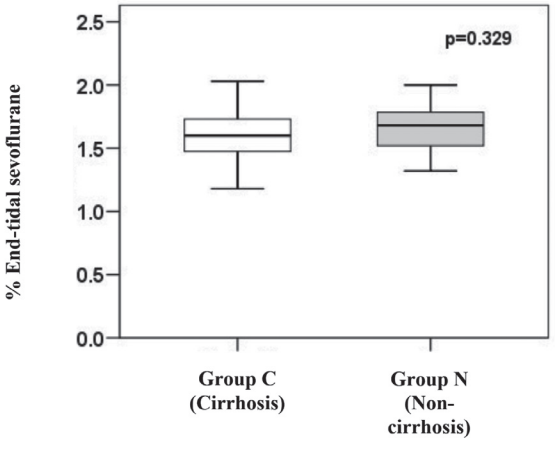



**Figure 1** End-tidal sevoflurane in cirrhotic and non-cirrhotic patients. Values are expressed as mean±SD (volume %)

**Table 1** Characteristics of cirrhotic and non-cirrhotic patients

| Variables | Cirrhosis (n=15) | Non-cirrhosis (n=15) | *P*-value |
|---|---|---|---|
| Age (years), mean±SD | 61.4±12.0 | 57.6±11.7 | 0.388 |
| Female/Male, n | 2/13 | 6/9 | 0.215 |
| BMI (kg/m$^2$), mean±SD | 23.6±3.4 | 23.2±4.2 | 0.758 |
| ASA physical status, n (%) | | | |
| I | 0 | 3 (20.0) | 0.224 |
| II | 3 (20.0) | 8 (53.3) | 0.128 |
| III | 12 (80.0) | 4 (26.7) | 0.009* |
| Diagnosis, n (%) | | | |
| Hepatocellular carcinoma | 14 (93.3) | 4 (26.7) | <0.001* |
| Colorectal liver metastasis | 0 | 6 (40.0) | 0.017 |
| Cholangiocarcinoma | 1 (6.7) | 2 (13.3) | 1.000 |
| Others | 0 | 3 (20.0) | 0.224 |
| Operation, n (%) | | | |
| Right hepatectomy | 8 (53.3) | 9 (60.0) | 1.000 |
| Left hepatectomy | 2 (13.3) | 4 (26.7) | 0.651 |
| Central hepatectomy | 1 (6.7) | 0 | 1.000 |
| Multi-segmentectomy | 1 (6.7) | 2 (13.3) | 1.000 |
| Epidural morphine (mg), mean±SD | 4.7±0.5 | 4.5±1.2 | 0.672 |
| Operative time (min), mean±SD | 312.2±75.9 | 389.4±109.9 | 0.033* |
| Hypotension, n (%) | 6 (40.0) | 7 (46.7) | 1.000 |
| Estimated blood loss (ml), median (IQR) | 500 (300, 650) | 500 (300, 700) | 0.900 |
| Bispectral index | 49.1±5.7 | 46.6±2.8 | 0.160 |

Value presented as mean±SD or median (IQR) and number (%).
P-value corresponds to independent t-test or Mann-Whitney U test and Fisher's exact test.
**P*-value < 0.05, BMI; body mass index

**Table 2** MAC of sevoflurane and sevoflurane consumption during the study

| Variables | Cirrhosis (n=15) | Non-cirrhosis (n=15) | *P*-value |
|---|---|---|---|
| MAC | 0.84±0.10 | 0.87±0.07 | 0.330 |
| Sevoflurane consumption (mL/h) | 13.64±2.10 | 11.03±1.89 | 0.001* |

Value presented as mean±SD, MAC; minimum alveolar concentration
**P*-value < 0.05

It is possible that the biotransformation of sevoflurane may be reduced in animals with liver fibrosis due to the depletion of cytochrome P-450.[14] Refaat et al. reported that the end-tidal concentration of sevoflurane required to achieve a constant entropy range of 40-60 and total sevoflurane consumption were significantly lower in cirrhotic liver compared with non-cirrhotic liver patients.[15] Wang et al. compared isoflurane concentration required to maintain a BIS index of 45-55 in three groups of patients. The outcome showed that end-stage liver disease patients undergoing liver transplantation required the least end-tidal isoflurane concentration followed by chronic hepatitis B with hepatocellular carcinoma patients undergoing hepatic resection. Otherwise healthy live liver donors required the highest concentration. They concluded that end-tidal isoflurane concentration requirements are different for patients with various liver status.[16]

Unlike other studies, the reason that we could not demonstrate the difference of sevoflurane requirement between groups may derive from two factors. Firstly, in previous studies, we have noticed that the mean age of cirrhotic patients was significantly higher. In Refaat et al. study, the mean age in cirrhosis group was 47.9±11.22 and in the control group was 29.7±8.52 ($P$<0.05).[15] In Wang et al. study, the mean age of end-stage liver disease patients and control group were 51.9±18.2 and 32.9±9.2 ($P$<0.05), respectively.[16] In our study, the mean age showed no significant difference among the study and control group. This could perhaps explain the difference in MAC requirements in the previous two studies since increasing age also decreases the MAC of sevoflurane at about 6% per decade[17,18], then elderly patients required lower anesthetic inhalation concentration compared to younger patients.

Secondly, according to the Barcelona Clinic Liver Cancer classification[19], curative hepatic resection in cirrhotic patients is recommended only in early tumor stages at Child class A without portal hypertension.[20] Our study based the diagnosis of liver cirrhosis on computerized tomography scan or magnetic resonance imaging together with clinical features, and biochemical results[21] under the same criteria as in previous study.[9] However, 10 out of 15 patients in cirrhosis group, the pathology reports from surgical tissue showed only mild or early stage liver fibrosis. These results might occur due to early detection and treatment of HCC in cirrhotic patients. Therefore, even advanced liver cirrhosis and portal hypertension are not considered as an absolute contraindication for hepatic resection. Our results demonstrated that major hepatic resections in cirrhosis were commonly performed in patients with relatively good liver function at Child class A. The effect of cirrhosis might not be present in this group of patients as opposed to cirrhosis Child B, C or in end stage liver disease patients. These two situations can possibly explain why our study could not find any significant difference of end-tidal sevoflurane between groups.

With regards to secondary outcome, the mean MAC of sevoflurane was not significantly difference between groups. The result was also correlated with the primary outcome in contrast to the mean of total sevoflurane consumption. Sevoflurane consumption (mL/h) was significantly lower in non-cirrhosis group. Since The study was not specifically powered for the secondary result, this result was not conclusive. Another hypothesis to this outcome derives from rostral

spread of epidural morphine. Since most of the patients the non-cirrhosis group were diagnosed with colorectal liver metastasis then the patients would be treated with neoadjuvant chemotherapy. The chemotherapy had toxic injury to the liver parenchymal which result in negative impact on surgical technique and duration of surgery.[12] Due to longer operative time in non-cirrhosis group, epidural morphine could reach supraspinal receptors during that period[22] and this may cause side effects such as sedation.[23] So, to maintain the same depth of anesthesia, the non-cirrhosis group might require less amount of inhalational anesthetic agent especially during at the end of surgery. Further investigations may require clarifying this hypothesis.

After hepatic resection, morphine pharmacokinetics are affected by reduced hepatic function and plasma clearance.[24] However, pain in open hepatic resection is categorized as severe pain and morphine is generally given during perioperative period. To provide better postoperative pain control, epidural morphine with local anesthetic is preferred in our hospital. Caution is still needed when using morphine in this patient group. None of the patients in both groups were found to have serious adverse effects such as over sedation or respiratory depression.

To the best of our knowledge, this is the first clinical study to investigate the effect of Child A cirrhosis on sevoflurane requirement under the same variable factors. Many variables alter the amount of inhalational anesthetic required during general anesthesia for example; age, temperature, sedative-hypnotic agents, and opioids. The strength of our study was these variables were not different between groups.

## Limitations

This study was conducted using a relatively small sample size. Moreover, there are also other factors that may limit our results. Firstly, in liver cirrhosis, there are many different score systems for grading the severity of liver fibrosis from surgical pathology, otherwise the results from surgical pathology may not represent all parts of the liver. This could be another limitation to our study. Secondly, in our non-cirrhosis group, most of the patients developed liver tumors from colorectal liver metastasis, cholangiocarcinoma or hepatic adenoma. There was no previous study about their effect on inhalational anesthetic requirement. Further studies may be required.

## Conclusion

Regarding inhalation anesthetic agents, our study could not show any significant difference in end-tidal sevoflurane requirement between Child-Turcotte-Pugh class A cirrhosis and non-cirrhosis. Nonetheless, we recommend anesthesiologists be cautious with over usage of inhalation agents, and BIS monitoring or other devices could be used to maintain adequate depth of anesthesia in patients with hepatic dysfunction. This is due to the higher risks of perioperative morbidity and mortality in cirrhotic patients compared to patients with normal hepatic function.

## References


1. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology. 2019;156:477-91.e1.
2. Omata M, Cheng AL, Kokudo N, et al. Asia-pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11:317-70.
3. Mansour A, Watson W, Shayani V, Pickleman J. Abdominal operations in patients with cirrhosis: still a major surgical challenge. Surgery. 1997;122:730-5.
4. Baron-Stefaniak J, Gotz V, Allhutter A, et al. Patients undergoing orthotopic liver transplantation require lower concentrations of the volatile anesthetic sevoflurane. Anesth Analg. 2017;125:783-9.
5. Ko JCH, Abbo LA, Weil AB, Johnson BM, Inoue T, Payton ME. Effect of orally administered tramadol alone or with an intravenously administered opioid on minimum alveolar concentration of sevoflurane in cats. J Am Vet Med Assoc. 2008;232:1834-40.
6. Donovan KL, Janicki PK, Striepe VI, Stoica C, Franks WT, Pinson CW. Decreased patient analgesic requirements after liver transplantation and associated neuropeptide levels. Transplantation. 1997;63:1423-9.
7. Farrell GC, Cooksley WG, Powell LW. Drug metabolism in liver disease: activity of hepatic microsomal metabolizing enzymes. Clin Pharmacol Ther. 1979;26:483-92.
8. Quero JC, Schalm SW. Subclinical hepatic encephalopathy. Semin Liver Dis. 1996;16:321-8.
9. Yin Y, Xiao H, Han J, Zhang W, Cheng J, Zhu T. Effect of the severity of liver dysfunction on the minimum alveolar concentration of sevoflurane responding to an electronic stimulation in cirrhotic patients. BMC Anesthesiol. 2016;16:98.
10. Petsiti A, Tassoudis V, Vretzakis G, et al. Depth of anesthesia as a risk factor for perioperative morbidity. Anesthesiol Res Pract. 2015;2015:829151.
11. Melloul E, Hubner M, Scott M, et al. Guidelines for perioperative care for liver surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. World J Surg. 2016;40:2425-40.
12. Chow FC, Chok KS. Colorectal liver metastases: an update on multidisciplinary approach. World J Hepatol. 2019;11:150-72.
13. Yin Y, Yan M, Zhu T. Minimum alveolar concentration of sevoflurane in rabbits with liver fibrosis. Anesth Analg. 2012;114:561-5.
14. Farrell GC, Zaluzny L. Microsomal protein synthesis and induction of cytochrome P-450 in cirrhotic rat liver. Aust J Exp Biol Med Sci. 1984;62:291-301.
15. Refaat E, Yassein T. Reduced sevoflurane consumption in cirrhotic compared to non-cirrhotic patients undergoing major hepatic surgery: during entropy monitored general anesthesia. Egypt J Anaesth. 2013;29:61-5.
16. Wang CH, Chen CL, Cheng KW, et al. Bispectral index monitoring in healthy, cirrhotic, and end-stage liver disease patients undergoing hepatic operation. Transplant Proc. 2008;40:2489-91.
17. Fragen RJ, Dunn KL. The minimum alveolar concentration (MAC) of sevoflurane with and without nitrous oxide in elderly versus young adults. J Clin Anesth. 1996;8:352-6.
18. Eger EI 2nd. Age, minimum alveolar anesthetic concentration, and minimum alveolar anesthetic concentration-awake. Anesth Analg. 2001;93:947-53.
19. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329-38.
20. Eguchi S, Kanematsu T, Arii S, et al. Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma. Brit J Surg. 2011;98:552-7.
21. Goodman ZD. Grading and staging systems for inflammation and fibrosis in chronic liver diseases. J Hepatol. 2007;47:598-607.
22. Bromage PR, Camporesi EM, Durant PA, Nielsen CH. Rostral spread of epidural morphine. Anesthesiology. 1982;56:431-6.
23. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth. 1995;42:891-903.
24. Rudin A, Lundberg JF, Hammarlund-Udenaes M, Flisberg P, Werner MU. Morphine metabolism after major liver surgery. Anesth Analg. 2007;104:1409-14.