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Research Article

Reduced sevoflurane consumption in cirrhotic compared to non-cirrhotic patients undergoing major hepatic surgery During entropy monitored general anesthesia

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KEYWORDS

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Abstract *Background:* There is evidence in literature that chronic hepatic patients need less anesthesia compared with healthy ones. Liver cirrhosis leads to a reduction in liver mass and hepatic blood flow with an effect on drug clearance and cardiovascular stability.
Aim: To evaluate sevoflurane consumption during entropy monitored general anesthesia in cirrhotic and non-cirrhotic patients during transition from consciousness to unconsciousness and throughout the procedure of major hepatic surgical procedures.
Patients and methods: Forty patients scheduled for major hepatic resection at the National Liver Institute, Menofiya University, Egypt, were studied prospectively and randomized into two equal groups. Group I (n. 20) cirrhotic patients (Child Pugh Grade A) with focal lesion, Group II (n. 20) healthy live liver donors undergoing major hepatectomies. Sevoflurane inhalational concentration was adjusted to achieve a state and response entropy of 40–60, and when RE increases 5–10 units above SE; more intravenous analgesics were given.
Results: Mean (SD) Sevoflurane consumption in Group II showed higher consumption 23.5 (3.23) ml, compared to Group I 16 (2.19) ml. Mean (SD) sevoflurane consumption after 4 and 6 h from induction also showed a lower value in Group I 10.7(1.94), 9(1.22) ml, than in Group II 17.2(1.69), 14.1(2.19) ml, respectively. Mean (SD) end tidal sevoflurane concentration was lower in Group I 1.4(0.12) after 2 h from induction than in Group II 1.7(0.11). After 4 and 6 h from induction Group I demonstrated a lower value compared to Group II ($P < 0.05$.). Mean blood pressure, heart rate,

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urine output and CVP showed no significant changes during maintenance between the two groups. *Conclusion:* This study demonstrated that cirrhotic patients require less sevoflurane consumption and lower end-tidal concentration to maintain general anesthesia with entropy guidance. This could also have an important impact on the economic costs when applied on a larger scale.

1. Introduction

Anesthesia is a balance between the amount of anesthetic drugs administered and the state of arousal of the patient, given that the intensity of surgical stimulation varies throughout surgery, and the hemodynamic effects of the anesthetic drugs may limit the amount that can be given safely, it is not uncommon for there to be critical imbalances between anesthetic requirements and anesthetic drug administration. Underdosing may be due to equipment failure or an error [1]. Conversely, inappropriate titration of the hypnotic components, leading to an excessive depth of anesthesia (DOA), might compromise patient outcome [2]. Patient movement in response to noxious stimulation remains an important sign of inadequate DOA, but is unreliable [3] and is suppressed by paralysis. Traditional clinical signs such as hypertension, tachycardia and lacrimation are unreliable indicators of DOA [4]. Monitoring anesthetic depth make it possible to administer the appropriate dose of anesthetics and prevent anesthetic awareness, side-effects of over-dosage, and economic and environmental waste. Therefore, anesthetic management, using proper anesthetic administration, is equally important as maintaining vital signs of the patient. Entropy monitoring allows for the quantification of cerebral neural activity. The increase and decrease in entropy scores are related to the level of consciousness under anesthesia. EEG entropy is an entropy monitor based on EEG analysis used in measuring hypnosis levels [5]. EEG-entropy has two signals: State entropy (SE) receives information from the brain waves and response entropy (RE) incorporates information from the frontal electromyography. SE is computed using EEG data from the previous 15 s, between 0.8 and 32 Hz, and shows the value in the range of 0–91. RE is computed from 32 to 47 Hz with 1.92 s, and reflects fast muscular activity from the frontal muscle, and shows the value in the range of 0–100. [6]

In Egypt, cirrhosis is mostly due to bilharzial peri-portal hepatic fibrosis or repeated viral attacks leading to chronic hepatitis. The death rate due to liver cirrhosis in Egypt is not exactly known due to deficient statistical evaluation [7].

Preoperative recognition of compensated or occult liver disease is important, because stresses of anesthesia and surgery can precipitate overt hepatic dysfunction in those patients. So, patients with liver disease pose major challenges in operating room and intensive care units. A comprehensive understanding of the liver problem is a must for doctors dealing with patients in these two locations [8].

In this study we maintained the appropriate anesthetic depth for patients undergoing entropy-monitored hepatic surgery where anesthetic depth was controlled by both titrating the concentration of the inhaled anesthetic–sevoflurane and entropy monitoring. We attempted to compare sevoflurane consumption and end-tidal concentration when using continuous infusion of sevoflurane in cirrhotics and non-cirrhotics undergoing major hepatic surgery.

2. Patients and methods

After obtaining written informed consent and approval of the local ethics and research committee at the Menofiya University, Egypt. This prospective randomised study was conducted at the Anaesthesia Department of the National Liver Institute, Menofiya University. It included forty patients from both sexes who underwent a major hepatic surgery.

Exclusion criteria included; patients with known neurologic or psychiatric disorders, chronic use of anticonvulsant or other centrally active medications, patients with clinically significant cardiovascular, respiratory or renal diseases, patients with long-term drug or alcohol abuse and patients with body mass index >40 (morbid obesity).

The forty patients were divided into two groups, each one contained twenty patients. Group (I); cirrhotic patients (Child Pugh Grade A) with hepatic focal lesion undergoing hepatectomy, Group (II); healthy live liver donors undergoing graft procurement.

On arrival to the operating theatre, standard monitors were applied. Normothermia was maintained by forced-air warming. After the skin of the forehead was carefully wiped with alcohol swab and then allowed to dry, the entropy disposable sensor (three separate wet gel electrodes) was positioned as recommended by the manufacturer entropy module of the S/5e Anaesthesia Monitor by GE Healthcare Finland (Datex-Ohmeda, Helsinki, Finland) in all groups. The sensor was applied on the forehead one inch (2–3 cm) above eyebrows. Number 1 at the midline of the forehead. Number 3 on the either template area between corner of eye and hairline. Number 2 in between the previous two electrodes. Sensor edges were pressed to assure adhesion.

Recording of the biosignal from the patient's forehead was started while the patient was awake. The impedance for the entropy sensor was checked and noted before induction. Baseline heart rate and mean arterial blood pressure were obtained in the operating room before induction of anesthesia.

After administration of 100% oxygen, anesthesia was induced with propofol 2 mg/kg IV (propofol dose was adjusted to achieve SE (40–60) and SE-RE difference less than 10). Fentanyl 2 μg/kg IV and rocuronium 0.6 mg/kg IV was administered to facilitate tracheal intubation. The patient was mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 30–35 mmHg. Followed by sevoflurane 2% (initial inspired concentration) in combination with air 50% in oxygen.

Intermittent bolus doses of rocuronium (0.05 mg/kg IV) were administered according to the results of the train of four (TOF). Subsequently, anesthesia was maintained with sevoflurane and fentanyl.

Entropy data includes, the state entropy (SE) (range from 0 to 91) and the response entropy (RE) (range from 0 to 100). RE becomes equal to the SE when there is no electromyographic activity. Recommended range for adequate anesthesia for both parameters is from 40 to 60, when SE increases above 60 the anesthetic drug dosage was increased. In contrast, if SE was in the recommended range, but RE increases 5–10 units above it, this is interpreted as a sign of uncovered nociception, and more intravenous analgesic medication was required.

During maintenance, anesthesiologists were instructed to adjust the sevoflurane concentration to keep SE, and RE values in the range of 40–60 by titrating 0.5 vol.% sevoflurane every 5 min. Intermittent bolus doses of fentanyl 1–2 μg/kg IV were given if the difference between RE and SE was more than 10 for more than 2 min.

At the end of surgery, in both groups, anesthesia was guided to achieve rapid recovery. Therefore, it was allowed to accept state entropy values >60 in the period 15 min before the end of surgery and the inhaled anesthetics was discontinued, and residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg IV and atropine 0.01 mg/kg IV.

Cases which needed massive blood transfusion and significant doses of rescue drugs were excluded from the study.

The mean arterial blood pressure, heart rate, SE, and RE values were recorded before induction of anesthesia, at 5 min intervals over 15 min period and at the end of surgery. The used dosage of propofol at induction was recorded. End-tidal sevoflurane, fentanyl dosage and sevoflurane consumption were monitored 2, 4 and 6 h after induction of anesthesia. Central venous pressure and the urine output were recorded every 2 h.

3. Statistical analysis

Statistical analysis was done on a personal computer using the IBM® SPSS® Statistics version 20 software (IBM® Corporation, Armonk, NY, USA).

Normality of quantitative data distribution was tested using the one-sample Kolmogorov–Smirnov goodness-of-fit test. Normally distributed quantitative data were presented as mean (standard deviation) and between-group differences were compared parametrically using the independent samples Student *t* test.

All *P* values are two-tailed. *P* values <0.05 were considered statistically significant.

4. Results

The demographic data analysis showed that healthy living donors (Group II) were significantly younger compared with patients in Group I. There were no statistical differences in the patient weight or sex distribution. (Table 1) There was no significant change between Group I and Group II regarding propofol consumption during induction (Table 1).

There was no significant differences between the 2 studied groups in mean arterial pressure and heart rate measurements at the preinduction time, during the follow up times of measurement at 5, 10 and 15 min after induction and at the end of surgery. $P > 0.05$ (Table 2).

RE and SE were maintained in both groups between 40 and 60, and there were no significant differences among subjects in both groups (Table 2).

Table 1 Clinical characteristics of the patients.

	G1	G2	*P*-value
	(*n* = 20)	(*n* = 20)	
Age (year)	47.9 ± 11.22	29.7 ± 8.52	<0.05
BMI (kg/m^2)	26.7 ± 3.96	25.7 ± 3.31	<0.05
Propofal induction Dose (mg)	156.6 ± 22.25	157.6 ± 25.42	<0.05
Duration of surgery	7.1 ± 0.3	7.5 ± 0.4	<0.05

Data are presented as mean ± SD. $P < 0.05$ is considered significant.

When assessing sevoflurane consumption in the two studied groups; there were significant changes after 2 h from induction in the studied groups. Group II showed a higher consumption 23.5 (3.23) ml, while Group I 16 (2.19) ml showed a lower consumption (Table 3).

Sevoflurane consumption after 4 h from induction showed a lower value in Group I 10.7 (1.94) ml, compared to Group II 17.2 (1.69) ml. Also after 6 h from induction Group I 9 (1.22) showed a lower consumption value compared to Group II 14.1 (3.02) ml.

End tidal sevoflurane; Group I showed a lower values after 2, 4 and 6 h from induction (1.4(0.12)%, 1.4(0.11)%, and 1.3(0.17)% respectively) compared to Group II (1.7(0.11)%, 1.6(0.07)% and 1.6(0.10)% respectively) (Table 3).

There was no significant change between the two studied groups in fentanyl consumption after 2, 4 and 6 h from induction $P > 0.05$ (Table 3).

Central venous pressure and urine output; showed no significant change between the two studied groups after 2, 4 and 6 h from induction $P > 0.05$ (Table 4).

5. Discussion

Maintaining anesthetic depth is essential during surgery to prevent awareness and overdosage. Judging the depth of anesthesia from observing the patient cardiovascular response and titrating the dose of anesthetics was a common practice for many years. The recent introduction of EEG-entropy as a monitor for the depth of anesthesia and hypnosis lead to a reduction in the incidence of unwanted perioperative events such as hypertension, tachycardia or awareness throughout general anesthesia [9] (see Table 5).

Entropy was used in the current study to monitor the titration of general anesthesia administration during hepatic resection surgery in cirrhotic and non-cirrhotic patients. Many previous studies on healthy liver patients reported the influence of the depth of anesthesia monitoring on the consumption of hypnotic drugs and few studies monitored the effect on cirrhotic patients.

Vakkuri et al. [10] stated that in sevoflurane-anesthesia, the appropriate depth of anesthesia has the entropy value of 40–60. In our study, sevoflurane concentration was adjusted so that the entropy value was maintained between 40 and 60. Comparisons of RE and SE between the two groups showed no significant differences, and they followed similar changes with time.

Our current results showed that the end-tidal concentration of sevoflurane to achieve a constant entropy range of 40–60

Table 2 Hemodynamics, state entropy and response entropy in both groups at the five measurement points.

Variable	T1	T2	T3	T4	T5	*P*-value
MAP (mmHg)						
GI	96.4 ± 3.34	94.3 ± 3.62	89.7 ± 3.81	86.7 ± 3.84	87.3 ± 3.22	< 0.05
GII	94.5 ± 3.41	92.9 ± 3.24	89.2 ± 3.51	86.7 ± 3.85	89.2 ± 3.52	
HR (beat/min)						
GI	87 ± 12.32	89 ± 12.30	82 ± 9.72	77 ± 9.08	87 ± 11.39	< 0.05
GII	92 ± 8.89	85 ± 8.91	80 ± 11.49	76 ± 10.87	89 ± 8.79	
State entropy (SE)						
GI	90 ± 0.63	61 ± 4.26	54 ± 6.58	42 ± 3.31	63 ± 4.22	< 0.05
GII	90 ± 0.99	63 ± 4.79	52 ± 5.37	41 ± 3.62	60 ± 3.61	
Response entropy (RE)						
GI	100 ± 0.00	64 ± 4.18	53 ± 6.96	42 ± 3.22	62 ± 5.61	< 0.05
GII	99 ± 0.63	65 ± 4.97	53 ± 5.62	41 ± 3.62	61 ± 4.20	

Changes of mean arterial pressure (MAP), heart rate (HR), state entropy (SE) and response entropy (RE) in GI (Group I, cirrhotic patients) and GII (Group II, healthy liver). Values are expressed as mean ± SD, *P*-value < 0.05 was considered statistically significant. Before the induction (T1), 5 min, 10 min and 15 min after induction (T2, T3 and T4) respectively, and at end of surgery (T5).

Table 3 Sevoflurane consumption, end-tidal sevoflurane and fentanyl at 2, 4 and 6 h after induction.

Variable	T1	T2	T3	*P*-value
Sevoflurane (ml)				
GI	16 ± 2.19	10.7 ± 1.94	9 ± 1.22	< 0.01
GII	23.5 ± 3.23	17.2 ± 1.69	14.1 ± 3.02	
ET-sevo				
GI	1.4 ± 0.12	1.4 ± 0.11	1.3 ± 0.17	< 0.01
GII	1.7 ± 0.11	1.6 ± 0.07	1.6 ± 0.10	
Fentanyl (μg)				
GI	140 ± 50.7	80 ± 56.0	60 ± 54.7	< 0.05
GII	153 ± 51.6	93 ± 59.3	63 ± 51.4	

Sevoflurone, end-Tidal sevoflurane and fentanyl in the two studied groups; GI (Group I, Cirrhotic patients) and GII (Group II, healthy liver) values are expressed as mean ± SD. *P*-value < 0.05 is statistically significant. The values are at 2, 4, and 6 h after induction (T1, T2, and T3 respectively).

Table 4 Central venous pressure and urine output, measured at 2, 4 and 6 h after induction in both groups.

Variable	T1	T2	T3	*P*-value
CVP (cmH_2O)				
GI	5.4 ± 0.9	5.6 ± 0.7	6.3 ± 1.2	< 0.05
GII	6.1 ± 1.2	6.1 ± 1.2	6 ± 0.65	
UOP (ml)				
GI	176 ± 24.1	178 ± 40.1	154 ± 45.6	< 0.05
GII	171 ± 32.9	173 ± 44.5	161 ± 25.8	

Central venous pressure (CVP) and urine output (UOP) in the two studied group GI (Group I, cirrhoic patients) and GII (Group II, healthy liver). Values are expressed as mean ± SD. *P*-value < 0.05 is considered significant. The values measured at 2, 4 and 6 h after induction (T1, T2 and T3) respectively.

Table 5 Liver functions in the two studied groups.

	GI	GII	*P*-value
Albumin (gm/L)	3.5 ± 0.2	3.8 ± 0.6	< 0.05
AST (iu/L)	51.3 ± 29.9	42.2 ± 20.46	< 0.05
ALT (iu/L)	51.03 ± 29.9	34.9 ± 27.4	< 0.05
INR	1.0 ± 0.7	1.0 ± 0.3	< 0.05
Bilirubin (mg/dl)	1.26 ± 0.67	1.19 ± 159	< 0.05

Data are presented as mean ± SD. $P < 0.05$ is considered significant AST, aspartate aminotransferase; ALT alanine aminotransferase; INR international normalized ratio.

was significantly different among the two studied groups. When compared with GI, the end-tidal sevoflurane concentration in GII was significantly lower from 2 h after anesthesia induction until the end of the operation. The results indicated that the worse the liver function, the lower end-tidal concentration of the sevoflurane was required to achieve the preset entropy level. Regarding sevoflurane consumption in the two studied groups; Group II showed the higher consumption, while Group I showed the lower consumption after 2, 4 and 6 h from induction. Therefore in our study, provided that there were no statistically significant differences between both groups regarding, weight, blood pressure or intraoperative temperature, the cirrhotic patients had the lower sevoflurane consumption and end-tidal concentration compared with healthy livers (GI, live liver donors) who required the higher sevoflurane consumption and end-tidal concentration to achieve sufficient anesthetic depth as monitored by the preset value of entropy during hepatectomy.

The results of the current study were similar to a study performed by Wang et al. [11], to assess factors influencing the end-tidal concentrations of isoflurane within a bispectral index (BIS) range of 45–55 among healthy live liver donors, chronic hepatitis B patients undergoing hepatectomy for hepatocellular carcinoma, and end-stage liver disease patients undergoing liver transplantation. The study showed that end-stage liver disease patients required the least end-tidal isoflurane concentration. Patients with hepatocellular carcinoma with cirrhosis required intermediate end-tidal isoflurane concentrations; healthy live liver donors required the highest end-tidal isoflurane concentrations to provide sufficient anesthetic depth. They concluded that liver function was the

only significant factor influencing the likelihood of lowering the end-tidal isoflurane concentration by 4 h after anesthesia induction.

Kang et al. [12], conducted a study on the relationship between inhalational anesthetic requirements and the severity of liver disease in liver transplant recipients according to three phases of liver transplantation. The study included fifty patients undergoing living donor OLT were divided into two groups: model for end-stage liver disease (MELD) score < 20 versus MELD score > or = 20. ET desflurane to maintain comparable anesthetic depth was significantly lower during the preanhepatic and anhepatic phases in the high-MELD than the low-MELD group, but there was no significant difference during the post reperfusion period. They concluded that OLT patients with high MELD scores showed less inhalational anesthetic requirements during the preanhepatic and the anhepatic periods than those with low MELD scores.

The mechanisms for these differences are not clear. It has been shown that, during inflammatory processes, cytokines may trigger opioid-induced antinociception in peripheral opioid receptors [13]. Interleukin 1 beta (IL-1_) or corticotropin-releasing factor (CRF) is capable of producing antinociception, which is believed to be caused by the release of endogenous opioids, such as β-endorphin, dynorphin A, and met-enkephalin.

In liver transplantation, posttransplantation require less analgesia for postoperative pain relief [14]. Whether there was less requirement of analgesic during the operation is not clear. The mechanism why posttransplantation recipients require less analgesia was studied by Donovan et al. in humans [14] and animals [15]. He found that among the pain-related neuromodulators, only metenkephalin plasma levels, not beta-endorphin and substance P plasma levels, were significantly increased both before and after liver transplantation when compared with a control operation, thereby, subsequently decreasing the analgesic requirement in the postoperative period [14,15]. In addition, inflammation caused by chemical injury to the liver, tissue inflammation, and even acute stress have been associated with increased plasma peptidase derivable metenkephalin levels, which subsequently modulate pain nociception [16]. Exogenous narcotics are known to reduce the MAC of sevoflurane [17]. Whether endogenous neuropeptides modulate the MAC of sevoflurane is not clear; it needs further biochemical studies.

The limitation of this study was the significant difference in age between the two studied groups which was inevitable because the current study compare between liver cirrhotic patients and healthy live donors of orthotopic liver transplantation; but this difference were not felt to impact the noted overall outcome of this prospective study.

In summary, during entropy monitored general anesthesia with values between 40 and 06, cirrhotic patients showed lower levels of sevoflurane consumption than non-cirrhotic patients. The end-tidal concentration requirements of inhalational anesthetics were lower for patients with impaired liver status. The use of entropy to monitor levels of end tidal inhalational anesthetics is helpful to avoid unnecessary high concentrations of general anesthetics for cirrhotic patients which will prevent the delay in recovery resulting from overdose and also to reduce cost during prolonged surgical procedures.

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