Entropy-guided end-tidal desflurane concentration during living donor liver transplantation

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ABSTRACT

Background: The three phases of living donor liver transplantation (LDLT) represent different liver conditions. The aim is to study the required end-tidal desflurane concentration (ET-Des) guided with entropy monitoring for the depth of anesthesia. **Methods:** After the Ethics and Research Committee approval, 40 patients were included in this prospective study. Anesthesia was maintained with Desflurane-O2-air. State entropy (SE) and Response entropy (RE) were kept between 40 and 60. **Results:** Age and Model for End-stage Liver Disease (MELD) score were 45±10 years and 15.43±3.92, respectively. ET-Des were significantly lower in the anhepatic phase (2.8±0.4%) than in the pre-anhepatic and neohepatic phases (3.3±0.3%, 3.47±0.3%, respectively, *P*<0.001). The SE and RE for pre-anhepatic, anhepatic, and neohepatic phases were (45.6±3.7, 47.4±3.2), (44.7±2.1, 46.4±2.04), and (46.1±3.3, 47.9±3.3), respectively, with no significant changes between the phases, *P* > 0.05. Total operative time was 651±88 minutes, and for each phase it was 276±11, 195±55, and 191±24 minutes, respectively. Significant changes were found in hemoglobin g/dl and hematocrit % between the three phases (10.28±1.5, 30.48±4.3), (9.45±1.34, 28.36±4.1), and (8.88±1.1, 26.63±3.5), *P*<0.05. The heart rate and mean blood pressures were stable despite the cardiac index demonstrated a significant reduction during the anhepatic phase (2.99±0.22) when compared to the pre-anhepatic and neohepatic phases (3.60±0.29) and (4.72±0.32), respectively, (*P*<0.05). There was a significant correlation between CI and ET-Des% (r=0.604, *P*<0.05). **Conclusion:** Inhalational anesthetic requirements differed from one phase to another during LDLT, with requirements being the least during the anhepatic phase. Monitoring of the anesthesia depth was required, to avoid excess administration, which could compromise the hemodynamics before the critical time of reperfusion.

Key words: *Desflurane, end tidal, entropy, liver transplantation*

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INTRODUCTION

Liver transplantation is now common all over the world. It is a surgical procedure in which the unhealthy liver is replaced with a new liver allograft.

Numerous studies have investigated the anesthetic requirements of hepatic patients. Wang *et al.*,[1] in their study to compare the anesthetic needs of patients with different hepatic statuses like healthy liver donors, chronic hepatitis B patients undergoing hepatectomy for hepatocellular carcinoma (HCC), and end-stage liver disease (ESLD) patients undergoing liver transplantation, within the Bispectral Index (BIS) range of 45-55, found that ESLD patients required the least end-tidal isoflurane concentration, healthy live liver donors required the highest end-tidal isoflurane concentration, and the compensated hepatic patients undergoing liver resection needed intermediate end-tidal isoflurane concentration, to provide sufficient anesthetic depth, as monitored by a target BIS of 45-55%.[1]

In another study Kang *et al.*,[2] concluded that anesthetic requirements differ between the hepatic patients according to the severity of their liver disease.[2]

The liver transplantation procedure has three phases. The pre-anhepatic phase, which extends from the abdominal incision to the vascular isolation and removal of the native liver, the anhepatic phase that begins with the portocaval

clamp and ends with perfusion of the graft, and the neohepatic phase that begins with reperfusion and ends with closure of the abdominal incision.[3]

Every phase has distinct situations concerning the hemodynamics, coagulation, blood loss, electrolytes, fluid management, acid–base status, and temperature, in addition to the different hepatic statuses between the three phases. On account of all the previous causes, the depth of anesthesia is suspected to be different between the three phases. Therefore, monitoring of anesthesia during Orthotopic Liver Transplantation (OLT) is considerable.

Blood loss, major fluid shift, and the common use of vasoactive drugs cause significant changes in the hemodynamics and limit its rule as a reliable clinical monitor of anesthetic depth, and consider the need of using a specific monitor for monitoring the depth of anesthesia.

Entropy is a recent form of processed electroencephalography (EEG). It was launched commercially in 2003, to monitor the depth of anesthesia. It has two parameters; the fast reacting Response Entropy (RE) and the more steady State Entropy (SE). State Entropy provides a measure of the current cortical state of the patient. Response Entropy reflects in addition the frontal electromyography (EMG) activity, so it is thought to be an indirect measure of the adequacy of anesthesia, as EMG activity may increase as a result of intense nociceptive stimulation and during decreasing levels of anesthesia. The recommended range for adequate anesthesia for both parameters is from 40 to 60.[4]

We designed this study to investigate the difference between the three phases of liver transplantation with regard to the inhalational anesthetic requirements guided by monitoring anesthesia depth with entropy.

METHODS

After obtaining the approval of the Ethics and Research Committee of the National Liver Institute, Menofia University, and written informed consents from the patients, 43 patients aged 17 to 53 years scheduled for the living donor liver transplantation procedure (LDLT), were prospectively studied.

The exclusion criteria were the presence of hepatic encephalopathy, preoperative neurological or psychiatric disorders, or other centrally active medications.

A standard anesthetic technique was performed, with routine monitoring of a five-lead electrocardiogram (EKG), pulse oxymetry, capnnography, continuous invasive arterial blood pressure (ABP) via radial artery, esophageal temperature, continuous central venous pressure via a right internal jugular vein catheter, fraction-inspired oxygen concentration, end-tidal desflurane concentration, urine output, nerve stimulator for neuromuscular blockade, transesophageal Doppler (cardio Q) for hemodynamic monitoring, rotational thromboelastometry (ROTEM), and entropy for monitoring the depth of anesthesia (Entropy module of S/5e Anesthesia Monitor by GE Health Care Finland [formerly Datex-Ohmeda, Helsinki, Finland]). The entropy sensor was disposable with three separate wet gel electrodes; it was positioned on the forehead as recommended by the instructions of the manufacturer.

Anesthesia was induced with intravenous propofol 2 mg/kg, fentanyl 2 μg/kg, and rocoroniunm 1 mg/kg to facilitate tracheal intubation. Next, the patient was mechanically ventilated to maintain an end tidal carbon dioxide partial pressure (ETCO2) between 30 and 35 mm Hg. Anesthesia was maintained with desflurane and O2 in air (Fi O2=50%), fresh gas flow (FGF) was kept at less than 2 L/minute. End-tidal desflurane concentration was adjusted so as to maintain the entropy parameters values (SE and RE), between 40 and 60. Intermittent boluses of intravenous fentanyl (1-2 μ/kg) were given if the difference between SE and RE was more than 10 for more than two minutes.

Intermittent bolus doses of rocuronium (0.05 mg/kg) were administered according to the results of the train-of-four.

Fluids and catecholamines were administered according to the hemodynamics, central venous pressure (CVP), corrected flow time (FTc), systemic vascular resistance (SVR) values.

Blood products were given, guided by laboratory and rotational thromboelastometry findings. Rapid infusion devices were available for emergency use.

Intraoperative normothermia was maintained using forced air warming blankets, intravenous fluid warming devices, and a heat moisture exchange filter (HMEF).

Extracorporeal venovenous bypass was never used. During each phase of the procedure, hemodynamics (heart rate (HR), arterial blood pressure (ABP), CVP, and cardiac index (CI)), nasopharyngeal temperature, entropy value, and end-tidal desflurane concentration were recorded at 15 minute intervals.

Statistical analysis was done using the IBM statistical package for social sciences (SPSS®) program version 19 for Windows. Data were presented as mean±SD and were analyzed using analysis of variance and the Bonferroni test for *post hoc* multiple comparisons, $P<0.05$ was considered significant.

RESULTS

This single-center prospective study was carried out in the hospital of the National Liver Institute, which is a tertiary center focusing on liver diseases. Forty-three patients started in this study, but the study was completed by only 40 cases; two cases were excluded because of massive intraoperative hemorrhage and another case did not complete the surgery due to multiple malignant peritoneal nodules.

Table 1 shows the patients' preoperative data, while Tables 2 and 3 show the duration of surgery, fluids, blood products infusion, and other intraoperative data. There were statistically significant differences in HR between the pre-anhepatic and anhepatic phases, and in the mean arterial blood pressure (MBP) between the anhepatic and neohepatic phases, however, all the values were within the clinically acceptable range. The cardiac index

changed significantly through all the phases of surgery and this was accepted in such a type of surgery. There was a positive correlation between CI and the end-tidal desflurane concentration (r=0.604, $P<0.01$). Figure 1 shows the entropy parameters, (SE and RE), during the three phases. It shows no significant changes and this was a target in this study. Figure 2 shows end-tidal desflurane concentrations over different phases; ET-Des was significantly lower in the anhepatic phase than in the other two phases, and no significant differences were found between the pre-anhepatic phase and the neohepatic phase. Hemoglobin and hematocrit showed significant differences between their values in the pre-anhepatic phase and the neohepatic phase, while the temperature did not show any significant change throughout the surgery and almost always kept above 36°C.

DISCUSSION

Unlike Wang *et al.*,[1] who compared the end-tidal

Table 1: Patients preoperative data

Age (year)	45±10.16
Weight (Kg)	78.08±11.11
MELD	15.43±3.92

MELD – Model for end-stage liver disease

Table 2: Duration of surgery and fluid infusion

Duration of procedure (minutes)	651±88
Pre-anhepatic phase (minutes)	276±111
Anhepatic phase (minutes)	195±55
Neohepatic phase (minutes)	191±24
RBCs (U)	4.69±3.28
FFP (U)	5.36±3.71
Albumin 5% (ml)	1613±568
Colloids (ml)	1983±1342
Crystalloids (ml)	7367±3245

RBCs – Packed red blood cells; FFP – Fresh frozen plasma

Table 3: Intraoperative data

Data	Phase			P
	Pre-anhepatic	Anhepatic	Neohepatic	
HR	91.24±7.51	99.18±13.14	97.88±14.77	*
MBP	76.44±8.24	71.50±8.65	77±9.24	†
CI	3.60±0.29	2.99±0.22	4.72±0.32	*†‡
Hb (gm)	10.28±1.50	9.45±1.34	8.88±1.12	‡
Ht (%)	30.48±4.34	28.36±4.16	26.63±3.59	‡
Temperature	36.29±0.22	36.13±0.21	36.25±0.24	
ET-Des (%)	3.33±0.31	2.81±0.40	3.47±0.33	*†
SE	45.65±3.72	44.70±2.13	46.10±3.34	
RE	47.40±3.29	46.45±2.04	47.90±3.31	

HR – Heart rate; MBP – Mean arterial blood pressure; CI – Cardiac index; Hb – Hemoglobin; Ht – Hematocrit; ET-Des – End-tidal desflurane concentration; SE – State entropy; RE – Response entropy; *Pre-anhepatic versus anhepatic, †Anhepatic versus neohepatic, ‡Pre-anhepatic versus neohepatic, $P <0.05$
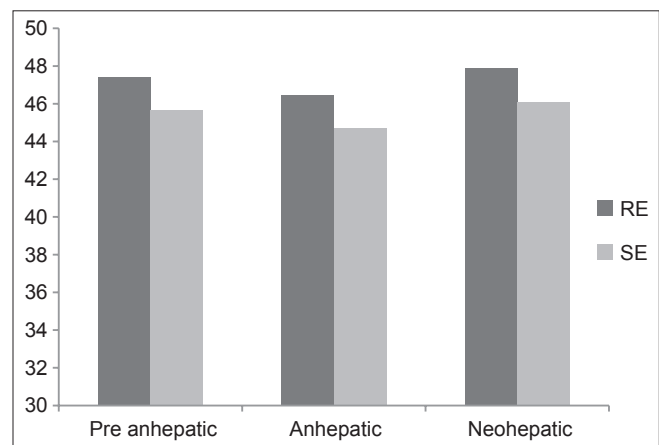

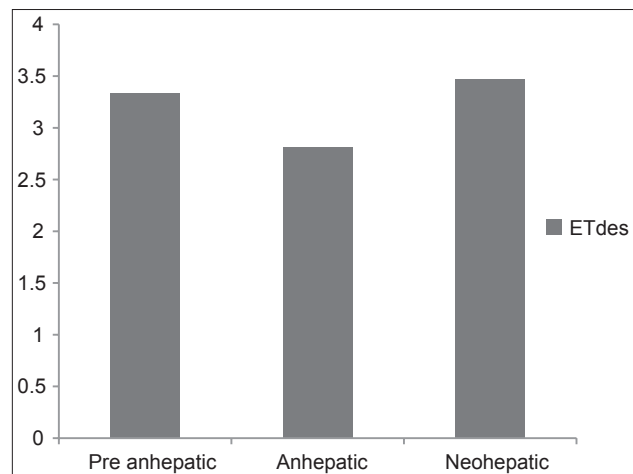**Figure 1:** Response entropy and state entropy during phases of transplantation

Figure 2: End-tidal desflurane concentration during phases of transplantation

isoflurane concentration (ETiso) among three groups of patients who differed in their liver status, to prove that the hepatic patients do need less inhalational anesthetic requirements than healthy individuals,[1] and unlike Kang *et al.,*[2] who compared the end-tidal desflurane (ET-Des) concentration between two groups of end-stage liver disease (ESLD) patients, who differed in the severity of their liver disease (patients were classified according to their score on the model for end-stage liver disease), to eventually prove that the more severely diseased hepatic patients need less end-tidal desflurane concentration, and hence, the inhalational anesthetic requirements are inversely proportionate with the severity of liver disease.[2]

We designed our study to compare the end-tidal desflurane concentration between the three phases of liver transplantation, within the same group of patients, to check if it differs from one phase to another, guided with entropy between 40 and 60.

We found that the ET-Des was the least during the anhepatic phase and it was significantly lower than the other two phases.

The obvious causes behind that are not apparent. Previous studies[1,2] explain their findings by changes in level of endogenous neuropeptides, such as, beta-endorphin, met-enkephalin, and substance P, as their levels are directly proportionate with the severity of liver disease.[1,2,5-8]

We cannot judge if this explanation is also applicable in this study on the same group of patients if the liver condition changes from one stage to another.

Factors that could affect MAC could not explain this difference between the anhepatic phase and the other two phases, as there was no significant difference in temperature over the study period, while changes in heart rate and mean blood pressure were clinically insignificant. However, the cardiac index changed significantly during the three phases of surgery and there was a positive correlation between CI and the end-tidal desflurane concentration, adding another possible contributing factor.

The unique pharmacokinetic and pharmacodynamic changes that occur during the anhepatic phase may have an additional rule.

Numerous studies showed results similar to those in our study, Tremelot *et al.,* in their study, compared the effect of the pre-anhepatic and the anhepatic phases on propofol target concentration during bispectral index (BIS)-guided target controlled infusion. The result showed that to maintain a stable BIS, the propofol target concentration

should be decreased during the anhepatic phase versus the dissection one. They explained their findings by a decrease in systemic clearance of propofol during the anhepatic phase, secondary to liver exclusion rather than cardiac output changes.[9]

Also Toprak, *et al.,*[10] found that the ETiso concentration needed in the anhepatic phase was significantly less than the other two phases of the procedure, to maintain a stable anesthetic depth monitored with a BIS range between 40 and 55.[10]

Schumann *et al.,*[11] in their study to determine whether the availability of BIS monitoring influences the anesthesia utilization pattern and affects anesthetic care and outcomes in OLT, found that the BIS group received less inhalational anesthesia during each phase of OLT compared to the control group. However, this difference was statistically significant only during the anhepatic phase and there was no difference in the BIS value between the different transplant phases, so this study confirmed the clinical observation that patients with ESLD undergoing OLT achieved an adequate anesthesia depth at low doses of inhalational anesthesia. They explained their findings by the effect of ESLD on the brain and the subclinical hepatic encephalopathy as well as the hepatically-induced hormonal alterations.[11]

CONCLUSION

Our study showed that employing Entropy between 40 and 60 to monitor the anesthesia depth resulted in less end-tidal desflurane concentration during the anhepatic phase than in the pre-anhepatic and the neohepatic phases. This alerted us to the value of using entropy to monitor the anesthetic depth, to tailor the anesthesia supplementation to the patient needs, especially in this critical phase, and to avoid anesthesia over depth, which could compromise the hemodynamics before the critical time of reperfusion, leading to exacerbation of its effects – all of this while ensuring an adequate depth of anesthesia.

REFERENCES

1. Wang CH, Chen CL, Cheng KW, Huang CJ, Chen KH, Wang CC, *et al.* Bispectral index monitoring in healthy, cirrhotic, and end-stage liver disease patients undergoing hepatic operation. Transpl Proc 2008;40:2489-91.
2. Kang JG, Ko JS, Kim GS, Gwak MS, Kim YR, Lee SK. The relationship between inhalational anesthetic requirements and the severity of liver disease in liver transplant recipients. According to three phases of liver transplantation. Transpl Proc 2010;42:854-7.
3. Steadman RH. Anesthesia for liver transplant surgery. Anesthesiology Clin N Am 2004;22:687-711.
4. Bruhn J, Lehmann L, Heiko Röpcke H, Bouillon TW, Hoeft A. Shannon Entropy Applied to the Measurement of the

Electroencephalographic Effects of Desflurane. Anesthesiology 2001;95:30-5.

5. Swain MG, Rothman RB, Xu H, Vergalla J, Bergasa NV, Jones EA. Endogenous opioids accumulate in plasma in a rat model of acute cholestasis. Gastroenterology 1992;103:630-5.

6. Thornton JR, Losowsky MS. Opioid peptides and primary biliary cirrhosis. BMJ 1988;297:1501-4.

7. Spivey JR, Jorgensen RA, Gores GJ, Lindor KD. Methionineenkephalin concentrations correlate with stage of disease but not pruritus in patients with primary biliary cirrhosis. Am J Gastroenterol 1994;89:2028-32.

8. 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.

9. Tremelot L, Restoux A, Paugam-Burtz C, Dahmani S, Massias L, Peuch C, *et al*. Interest of BIS monitoring to guide propofol infusion during the anhepatic phase of orthotopic liver transplantation. Ann Fr Anesth Reanim 2008;27:975-8.

10. Toprak HI, Sener A, Gedik E, Uçar M, Karahan K, Aydogan MS, *et al*. Bispectral Index monitoring to guide end-tidal isoflurane concentration at three phases of operation in patients with end stage liver disease undergoing orthotopic liver transplantation. Transpl Proc 2011;43:892-5.

11. Schumann R, Hudcova J, Bonney I, Cepeda MS. Availability of anesthetic effect monitoring: Utilization, intraoperative management and time to extubation in liver transplantation. Transpl Proc 2010;42:4564-6.

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