Original Article

Comparison of bispectral index targeted end-tidal concentration of desflurane during three phases of orthotopic liver transplantation

Address for correspondence:
Dr. Nitin Sethi,
Department of
Anaesthesiology, Pain and
Peri-Operative Medicine,
Sir Ganga Ram Hospital,
New Delhi - 110 060, India.
E-mail: nitinsethi77@yahoo.
co.in

Gyanendra Kumar, Nitin Sethi, Deepanjali Pant, Jayashree Sood, Amarjeet Singh, Shashank Pandey, Amitabh Dutta
Department of Anaesthesiology, Pain, and Perioperative Medicine, Sir Ganga Ram Hospital, New Delhi, India

ABSTRACT

Background and Aims: Reduced inhalational anaesthetic requirement in end-stage liver disease during living donor orthotopic liver transplantation (LD-OLT) is due to increased endogenous opioids. This study evaluated the changes in bi-spectral index (BIS) monitored end-tidal desflurane (ET_{Des}) requirements during 'dissection', 'anhepatic', and 'neohepatic' phases of LD-OLT. **Methods:** This prospective, cohort study included 40 adults undergoing LD-OLT under general anaesthesia (GA). All patients received BIS-guided desflurane GA. ET_{Des} requirements in three phases of LD-OLT (primary objective); relationship between inhalational anaesthetic requirements and severity of liver disease; and effect of changes in mean arterial pressure (MAP) and body temperature on ET_{Des} concentration for all three phases were also evaluated. **Results:** ET_{Des} during the 'dissection' phase (2.92 ± 0.65%) was > 'anhepatic' (2.68 ± 0.85%, $P = 0.049$) and 'neohepatic' phases (2.58 ± 0.71%, $P = 0.005$). Patients with model of end-stage liver disease (MELD) score < 20 returned significantly greater ET_{Des} than those with MELD score ≥20 during the 'dissection' (MELD <20: 3.11 ± 0.49%; MELD ≥20: 2.58 ± 0.77%, $P = 0.01$) and 'anhepatic'(MELD <20: 2.96 ± 0.76%; MELD ≥20: 2.17 ± 0.79%, $P = 0.003$) phases. A positive correlation was observed between ET_{Des} (r = 0.584, $P = 0.001$) and temperature in the 'dissection' phase only. **Conclusion:** In patients undergoing LD-OLT, BIS monitoring guidance of depth of desflurane GA suggests lower desflurane requirements during 'anhepatic' and the 'neohepatic' phase of surgery. Also, the desflurane requirement is greater in patients with lesser severity of liver disease.

Key words: Bispectral index, desflurane, liver transplant

INTRODUCTION

Orthotopic liver transplantation (OLT) has evolved as a definitive treatment prospect for patients with end-stage liver disease (ESLD).[1] Increased plasma levels of endogenous neuropeptides in ESLD patients reduces analgesic requirements[2] and may lower inhalational anaesthetic requirement.[3]

Inhalation anaesthetic, and desflurane has a fast-in-fast-out pharmacokinetic profile.[4] It is preferable during hepatic surgery as it undergoes minimal hepatic metabolism and preserves the splanchnic blood flow and hepatic oxygen delivery.[5] The evidence on its profile during OLT is limited to a couple of studies.[6,7]

Liver transplantation consists of three distinct phases: the 'dissection' phase, 'anhepatic' phase, and 'neohepatic' phase. Typically, decrease in inhalation anaesthetic requirement is more demonstrable during the 'anhepatic' phase than the 'dissection' or 'neohepatic' phase.[6,8]

Bispectral index monitoring (BIS) measures anaesthetic depth based on processed electroencephalograph. A BIS value between 40-60 indicates adequate depth.[9] Variations in anaesthetic requirements during the respective phases of transplant[6,8] makes monitoring anaesthetic depth an essential prerequisite.

This prospective clinical study evaluated changes in BIS-monitored end-tidal desflurane concentration during the three phases of living donor orthotopic liver transplantation (LD-OLT).

METHODS

After Institutional Ethics Committee approval and written informed consent, 40 patients with chronic ESLD, aged 18-65 years, of either sex, belonging to American Society of Anesthesiologists' (ASA) physical status III/IV, who were scheduled for undergoing living donor orthotopic liver transplantation (LD-OLT) were included in this single-arm, prospective, cohort study. The study duration was 15 months and study period was from 24th February 2015 to 5th April 2016. Patients with incumbent/acute hepatic encephalopathy (grade II-IV), acute hepatic failure, hepato-renal syndrome, preoperative requirement of mechanical ventilation, and where intraoperative veno-venous bypass was indicated were excluded from the study.

The changes in BIS-monitored end-tidal desflurane concentration during three phases of living donor orthotopic liver transplantation (LD-OLT) (primary objective); and relationship i) between inhalational anaesthetic requirement and severity of liver disease, and ii) effect of changes in mean arterial pressure and temperature on end-tidal desflurane concentration (secondary objectives); were evaluated.

The serum creatinine, serum bilirubin, and international normalised ratio (INR) of the patients was determined a day prior to the surgery to calculate the model for end-stage liver disease (MELD) score. MELD scoring was undertaken to determine preoperatively, the severity of disease. Patients with MELD score <20 were considered to have a less severe liver disease as compared to those with a MELD score >20.[6]

A secured venous access was established and routine monitoring (pulse-oximetry, electrocardiography, and non-invasive blood pressure) was applied. Before induction of anaesthesia, a BIS sensor (Covidien Inc., Mansfield, USA), along with BIS monitoring module (Model DSC-XP, Aspect medical system, USA) was applied over the patient's forehead for monitoring depth-of-anaesthesia.

Anaesthesia was induced with intravenous fentanyl citrate 2-μg/kg[10] and thiopentone sodium 5-mg/kg. Atracurium besylate 0.6-mg/kg was administered intravenously and trachea was intubated with appropriate sized cuffed endotracheal tube (size: 8.0 mm ID: males; size: 7.0 mm ID: females). Intraoperative ventilation was established as per a predefined strategy (volume controlled ventilation, tidal volume-8 ml/kg, ventilation frequency-14, I: E = 1:2). Intravenous infusion of fentanyl citrate (1-μg/kg/hour)[10] and atracurium besylate (5-10 μg/kg/min) was continued throughout the duration of surgery.

The end-tidal desflurane concentration, capnography, nasopharyngeal temperature, and urine output monitoring was instituted. Advanced haemodynamic (direct arterial blood pressure, central venous pressure, minimally invasive cardiac output) and coagulation (thromboelastography) monitoring was instituted after induction of anaesthesia. Serial arterial blood gas analysis was performed as per Institutional protocol for LD-OLT. For maintaining intraoperative temperature forced air warming blankets and intravenous fluid warmers were used.

After induction of anaesthesia, desflurane vaporizer dial concentration was set at 6% and a high flow gas delivery (4 liter/min: oxygen: air- 1:3) was initiated till a BIS score was <50. Then the flow of gases was adjusted to low-flow delivery (0.8 liter/min: oxygen-0.3 liter/min; air-0.5 liter/min) and the desflurane dial concentration was set at 8-percent. Thereafter, throughout the LD-OLT, end-tidal desflurane concentration was continuously adjusted to maintain a target BIS score (40-60).

Ventilation was adjusted (minute ventilation was targeted and change in ventilator rate was used) to maintain end-tidal CO_2 between a pre-specified (35-40 mmHg) range. Vasopressors (noradrenaline, vasopressin) were used to maintain mean arterial pressure above 70 mmHg as and when indicated. Intraoperative blood loss was compensated with transfusion of packed red blood cells. The trigger for blood transfusion was set as per standard Institution protocol at a haemoglobin of 8.0 gm % or below. Any coagulation abnormality demonstrated on the ongoing thromboelastograph (TEG) was corrected using fresh

frozen plasma, platelet apheresis or cryoprecipitate as deemed appropriate.

End-tidal desflurane concentration, BIS scores, haemodynamic parameters (heart rate, invasive blood pressure, cardiac output [CO], systemic vascular resistance [SVR], stroke volume variation [SVV]), and nasopharyngeal temperature were recorded at 15-minute interval during the three phases LD-OLT.

At the end of surgery all patients were shifted to multi-organ transplant intensive care unit for elective ventilation.

Based on a previous study[7] where end-tidal desflurane concentration was significantly lower in the 'anhepatic' phase (2.8 ± 0.4%) than 'pre-anhepatic' (3.3 ± 0.3%) and 'neohepatic' phases (3.47 ± 0.3%) ($P < 0.001$) of transplantation; a sample of 40 patients was calculated with an effect size of 0.71 for end-tidal desflurane concentration during the three phases of liver transplantation on a two-sided significance level of 0.05%, and at a power of 80-percent.Statistical analysis was performed using SPSS statistical package (version 17.0; SPSS Inc., Chicago, IL, USA) and included comparison of primary and secondary outcome variables. Continuous variables are presented as mean $\pm$ SD and categorical variables as absolute numbers and percentage. Changes in end-tidal desflurane concentration during the three phases of OLT (primary outcome variable) and end-tidal desflurane concentration in the three phases of OLT in patients with MELD score <20 and MELD score >20 (secondary outcome variable) were analyzed using repeated measures analysis of variance (ANOVA) followed by Bonferroni's *post hoc* testing. Spearman's correlation was used between end-tidal desflurane concentration, temperature, and mean arterial pressure during different phases of LD-OLT (secondary outcome variable). A *P* value less than 0.05 was considered statistically significant.

RESULTS

All the recruited patients ($n = 40$) met the study end-points and were considered for final analysis. The most common etiology for liver transplant was Hepatitis C virus CLD (32.5%). While the mean modified Child-Pugh's score for the patients was $10.97 + 1.71$, and the mean MELD score was $18.15 + 5.87$ [Table 1]. While there were 26 patients (65%) with a MELD score of <20, 14 patients (35%) had >20 MELD score.

Table 1: Demographic profile	
Age (year)	47.15±9.67
Sex (male:female)	38:2
Height (cm)	164.62±8.55
Weight (kg)	65.91±12.34
Etiology of Liver Dysfucntion	
Alcoholic liver disease	09 (22.5%)
Hepatitis C virus related CLD	13 (32.5%)
Cryptogenic liver disease	08 (20%)
Hepatitis B virus related CLD	08 (20%)
Primary biliary cirrhosis	01 (2.5%)
Nonalcoholic Steatohepatitis	01 (2.5%)
Liver Disease Severity Scoring	
Modified Child- Pugh's score	10.97±1.71
MELD score	18.15±5.87
Time Duration of 3 Phases of Surgery	
Dissection phase (minutes)	305.95±90.12
Anhepatic phase (minutes)	200.80±42.78
Neohepatic phase (minutes)	174±45.69

CLD – Chronic Liver Disease; MELD – Model for End -stage Liver Disease, Values expressed as mean±S.D and frequency (%)

While, the overall end-tidal desflurane concentration in the 'dissection phase' ($2.92 + 0.65$%) was significantly greater than that in the 'anhepatic' ($2.68 + 0.85$%, $P = 0.049$) and 'neohepatic' phase ($2.58 + 0.71$%, $P = 0.005$); it was comparable for the 'anhepatic' and 'neohepatic' phase ($P = 0.93$). Also, the corresponding overall BIS values were significantly higher in the 'dissection' phase (51.10 ± 5.95) as compared to the 'anhepatic' (45.01 ± 4.39, $P = 0.001$) and 'neohepatic' phase (45.73 ± 4.10, $P = 0.001$).

As per the severity of liver disease, the patients with MELD <20 returned significantly greater end-tidal desflurane concentration in the 'dissection' phase ($3.11 + 0.49$%) than the 'neohepatic' phase ($2.72 + 0.57$%, $P = 0.004$). However, in patients with MELD >20, no difference was found in the end-tidal desflurane concentration across the three phases of LD-OLT. In patients with MELD <20 and MELD >20, BIS values were significantly higher in the 'dissection' phase as compared to anhepatic' or 'neohepatic' phase [Table 2].

Patients with MELD < 20 returned significantly greater end-tidal desflurane concentration in the 'dissection' phase ($3.11 + 0.49$%) when compared to those with MELD >20 ($2.58 + 0.77$%, $P = 0.01$). Similarly, in the 'anhepatic' phase, the end tidal desflurane concentration in patients with MELD < 20 ($2.96 + 0.76$%) was significantly higher than the patients with MELD >20 ($2.17 + 0.79$% ($P = 0.003$). However, the end-tidal desflurane concentration in the 'neohepatic' phase in patients with MELD <20 ($2.72 + 0.57$%) was

Table 2: Comparison of intraoperative end-tidal desflurane concentration and BIS during three phases of live-donor liver transplant									
		Baseline	Dissection phase (DP) %	Anhepatic phase (AP) %	Neohepatic phase (NP) %	*P*			
						DP v/s AP	DP v/s NP	AP v/s NP	Overall
Overall (*n*=40)	Et-Des	-	2.92±0.65	2.68±0.85	2.58±0.71	0.049	0.005	0.93	0.87
	BIS	96.20±1.71	51.10±5.95	45.01±4.39	45.73±4.10	0.001	0.001	0.52	0.001
MELD <20 (*n*=24)	Et-Des	-	3.11±0.49	2.96±0.76	2.72±0.57	0.54	0.004	0.28	0.24
	BIS	95.85±1.69	50.54±3.86	45.09±3.94	45.93±3.67	0.001	0.001	0.78	0.005
MELD ≥20 (*n*=16)	Et-Des	-	2.58±0.77	2.17±0.79	2.32±0.87	0.13	0.74	0.74	0.05
	BIS	96.86±1.61	52.14±8.70	44.86±5.30	45.37±3.93	0.008	0.02	>0.99	0.001

MELD – Model for End -stage Liver Disease; Et-Des – End-tidal desflurane concentration, Values expressed as mean±S.D, *P*<0.05 significant

comparable to patients with MELD >20 (2.32 + 0.87%, *P* = 0.07). The BIS values were significantly lower during the 'dissection' phase in patients with MELD <20 (50.54 ± 3.86) as compared to patients having MELD >20 (52.14 ± 8.70, *P* = 0.02) but were comparable during the 'anhepatic' and 'neohepatic' phase [Table 3].

Overall, the heart rate in the 'dissection' phase was significantly less than that in 'anhepatic' phase (*P* = 0.001) and the 'neohepatic' phase (*P* = 0.001). However, it was comparable between the 'anhepatic' and 'neohepatic' phase (*P* = 0.15). The mean arterial pressure (MAP) was comparable across the three phases of LD-OLT (*P* = 0.88).While the cardiac output in the 'neohepatic' phase was significantly more than in the 'dissection' phase (*P* = 0.001) and 'anhepatic' phase (*P* = 0.001), the SVR in the 'neohepatic' phase was significantly lower when compared to the 'dissection' and 'anhepatic' phase (*P* = 0.001). The SVV in the 'anhepatic' phase was significantly more than that in the 'dissection' (*P* = 0.001) and the 'neohepatic' phase (*P* = 0.001). Notably the SVV was significantly greater for 'dissection' phase than in 'neohepatic' phase (*P* = 0.02) [Table 4].

The temperature in the dissection phase (36.0 + 0.4℃) was significantly less than compared to the 'anhepatic' (36.7 + 0.4℃) (*P* = 0.001) and 'neohepatic' phase (36.8 + 0.4℃) (*P* = 0.001) but was comparable between 'anhepatic' and 'neohepatic' phase (*P* = 0.14).

A positive correlation was observed between end-tidal desflurane concentration (r = 0.584, *P* = 0.001) and temperature in the 'dissection' phase. No correlation was found between end-tidal desflurane concentration and MAP in any of the phases.

DISCUSSION

The results of our study revealed a lower end-tidal desflurane requirements during the 'anhepatic' and

Table 3: Comparison of end-tidal desflurane concentration and BIS between patients with MELD <20 and MELD ≥20			
	MELD <20 (*n*=26)	MELD ≥20 (*n*=14)	*P*
Baseline			
Et-Des	-	-	-
BIS	95.85±1.69	96.86±1.61	0.07
Time Duration (min)	-	-	-
Dissection phase			
Et-Des	3.11±0.49%	2.58±0.77%	0.01
BIS	50.54±3.86	52.14±8.70	0.02
Time Duration (min)	298.42±76.01	319.93±113.70	0.48
Anhepatic phase			
Et-Des	2.96±0.76%	2.17±0.79%	0.003
BIS	45.09±3.94	44.86±5.30	0.32
Time Duration (min)	195.23±43.56	211.14±40.81	0.26
Neohepatic phase			
Et-Des	2.72±0.57%	2.32±0.87%	0.07
BIS	45.93±3.67	45.37±4.93	0.27
Time Duration (min)	175.27±40.63	171.64±55.49	0.81

MELD – Model for End -stage Liver Disease; Et-Des – End-tidal desflurane concentration, Values expressed as mean±S.D, *P*<0.05 significant

'neohepatic' phase than the 'dissection' phase of the LD-OLT. Anaesthesia delivery titrated to continuous depth-of-anaesthesia monitoring facilitates precise administration of anaesthetic drugs,[11] enhances recovery from anaesthesia,[12] and decreases haemodynamic perturbations.[13]

Generally, inhalation anaesthetic administration is titrated to MAC, a factor directly proportional to the end-tidal concentration of the inhalational agent.[14] Alternatively, intraoperative BIS monitoring allows end-tidal anaesthetic vapour concentration to be titrated to achieve a specified target BIS score to achieve and sustain adequate anaesthetic depth during surgery.[15]

The end-tidal isoflurane concentration required to maintain an adequate anaesthesia depth has been shown to be highest in healthy live liver donors, intermediate in patients with hepatocellular carcinoma, and the least in patients with ESLD.[16] This points towards a plausible relation between severity

Table 4: Intraoperative haemodynamic parameters						
	Dissection phase (DP)	Anhepatic phase (AP)	Neohepatic phase (NP)	P			
				DP v/s AP	DP v/s NP	AP v/s NP	Overall
Heart rate (beats/min)	95±13.01	105.43±16.30	102.17±14.38	0.001	0.001	0.15	0.11
MAP (mmHg)	79.19±8.23	77.06±8.50	76.76±8.70	0.14	0.08	>0.99	0.88
Cardiac output (l/min)	7.43±1.84	7.41±1.88	8.34±1.90	>0.99	0.001	0.001	0.312
SVR (dyn/s/cm^5)	829.29±233.22	849.25±261.29	730.24±212.39	>0.99	0.001	0.001	0.001
SVV (ml/beat)	9.66±2.62	11.04±3.93	8.48±2.57	0.03	0.02	0.001	0.001

MAP – Mean arterial pressure; SVR – Systemic vascular resistance; SVV – Stroke volume variation, Values expressed as mean±SD, *P*<0.05 significant

of liver dysfunction and anaesthesia requirements. The mechanism proposed for decreased anaesthetic requirements in patients with affected liver is the presence of increased levels of endogenous opioid neuropeptides (metenkephalin, beta endorphin, and substance *P*) which have central and peripheral analgesic effects. Heightened levels of endogenous opioids also contribute to the alteration in pharmacokinetic and pharmacodynamics drug profile in patients with liver disease.[3,17]

A study which analysed end-tidal isoflurane concentration during the three phases of orthotopic liver transplant revealed lowest requirement during the 'anhepatic' phase (0.58%) as compared to the 'dissection' (0.61%), and 'neohepatic' phase (0.63%).[8]

Another study involving entropy-guided desflurane anaesthesia for LD-OLT reinforced the evidence that end-tidal desflurane concentration is significantly lower in the 'anhepatic' phase (2.8 ± 0.4%) when compared to the 'dissection' (3.3 ± 0.3%) and 'neohepatic' phase (3.47 ± 0.3%).[7]

However, in contrast our study reported lower end-tidal desflurane requirements both during the 'anhepatic' phase (2.68 ± 0.85%) and 'neohepatic' phase (2.58 ± 0.71%) as compared to the 'dissection' phase (2.92 ± 0.65%). The lower desflurane requirements in the 'neohepatic' phase in our study differs from those reported in previous studies[7,8] and could be attributed to a delay in achieving optimal to graft function and consequently, gradual recovery of endogenous neuropeptides metabolism. Therefore, without a structured long-term follow-up, it is difficult to establish perpetual correlation between desflurane requirements and graft function during the 'neohepatic' phase.

The severity of liver dysfunction as assessed by MELD scoring also contributes to variability in inhalational anaesthetic requirement during LD-OLT. End- tidal desflurane concentration required to achieve a target

BIS of 40-60 has been shown to be significantly higher in patients with MELD score <20 during the dissection and anhepatic phase as compared to patients with MELD score >20.[6] In our study the end-tidal desflurane concentration was significantly more in patients with lower MELD score during the 'dissection' and 'anhepatic' phase compared to those with high MELD score. Although the values were comparable during the 'neohepatic' phase it was higher patients having a lower MELD score. The findings from our study reinforces the link between increased liver disease severity and corresponding decrease in anaesthetic requirement.

Temperature regulation and haemodynamic management are the two important non-disease physiological factors which can impact anaesthetic requirements in patients undergoing LD-OLT.[18,19] During LD-OLT, while acute hypotension is not uncommon owing to sudden massive bleeding and a low SVR;[20] difficult-to-manage hypothermia occurs because of the nature of surgery (prolonged, open, abdominal) and the iatrogenic effect of a cold preserved graft.[21] In our study, MAP was comparable across the three phases of surgery with pressure remaining above 75 mm Hg and no correlation was found between MAP and end- tidal desflurane concentration. Although a temperature differential was noted ('dissection phase': 36.0 ± 0.4°C; 'anhepatic' phase: 36.7 ± 0.4°C; and 'neohepatic' phase: 36.8 ± 0.4°C), it remained around 36°C across the three phases of surgery. The paradoxical low temperature versus high anaesthetic usage witnessed in the 'dissection' phase may be attributed to the dynamics of rate of fall of temperature in the face of increasing end-tidal anaesthetic concentration (obligate hypothermia following GA) and progressive decrease in temperature due to heat loss (radiation, convection) secondary to large laparotomy.

The study suffered from a few possible limitations (given below) that may impact clinical significance of this study. First, though unlikely, the use of fixed-dose

fentanyl [pre-induction phase (2-μg/kg); intraoperative period (1-μg/kg/hr)] may have accounted for a decrease in end-tidal desflurane concentration[22,23] for achieving equi-BIS status across the three phases of LD-OLT, and consequently, confounded the results. Second, the clinical utility of the knowledge of difference in end-tidal concentration during three stages of LD-OLT cannot be grounded unless compared with control group wherein depth-of-anaesthesia monitoring is not used routinely. Third, since we did not measure endogenous neuropeptide levels, the significance of the findings (difference in end-tidal concentration of sevoflurane during three phases of LD-OLT) cannot be translated to advantage in clinical practice. Finally, for our study objectives were focused mainly around ascertaining the difference in end-tidal concentration of inhalation anaesthetic during three phases of LD-OLT; the postoperative parameters (intraoperative awareness recall, postoperative delirium) representative of post-surgery cognitive recovery were not assessed.

CONCLUSION

BIS-monitoring facilitated depth of desflurane anaesthesia in patients undergoing LDLT showed reduced requirements during 'anhepatic' and the 'neohepatic' phase of surgery. Also, the desflurane requirement was greater in patients with less severe liver disease. Although, the implications of clinically small but statistically significant difference in the end-tidal desflurane concentration during three phases of LDLT in our study are not clearly known, the evidence has a potential to bolster precision delivery of desflurane during the three phases of LDLT, which can be translated into fast tracking of recovery of patients undergoing liver transplant surgery.

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Conflicts of interest
There are no conflicts of interest.

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