Effects of Thoracic Epidural Anesthesia on Liver Blood Flow and Indocyanine Green Clearance Test in Living-Donor Liver Transplantation: A Prospective, Randomized, Double-Blind Study

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ABSTRACT

Background. Donors are volunteers without any health problems. Therefore, the anesthetic management of donor safety is an important issue. Our aim in this study was to compare thoracic epidural anesthesia and general anesthesia effects on liver blood flow by means of liver function tests and indocyanine green and compared with living-donor liver transplantation.

Methods. Subjects were divided into 2 equal groups: the control group (group I) and the epidural block group (group II, closed envelope method). In group II patients, the epidural catheter was inserted at the T_{6-8} level. In all patients, anesthesia was standardized with the use of lidocaine, fentanyl, and thiopental. Indocyanine green clearance test values before general anesthesia (T0), after induction of general anesthesia (T1), after transection (T2), and at postoperative 24 and 72 hours were recorded. Simultaneously, hemoglobin, hematocrit, platelet count, prothrombin time (PT), international normalized ratio (INR), total bilirubin, direct bilirubin, albumin, aspartate transaminase, and alanine transaminase values were analyzed.

Results. Plasma disappearance rate (PDR) and retention at 15 minutes (R15) of indocyanine green were not statistically significant difference between groups ($P > .05$). Intragroup comparison of PDR and R15 values at times T1, T2, T3, and T4 showed that the values at T0 were statistically significant ($P < .05$). PT and INR values were significantly different for all times within each group ($P < .05$). It was concluded that the use of thoracic epidural anesthesia has no effect on global liver function and liver-related liability tests in patients undergoing elective liver donor surgery.

LIVER transplantation is the only opportunity in the treatment of patients with end-stage liver failure. Donors are volunteers with no health problems. Therefore, safety of donors is the most important issue in the management of anesthesia [1].

Hepatic hypoperfusion is an important factor in perioperative liver failure. In addition, hypoperfusion is suggested to initiate or contribute to systemic inflammatory response syndrome. Blocking of thoracic efferent sympathetic fibers results in regional arterial dilatation and regional blood flow. However, hypotension is the result of decrease in systemic vascular resistance, and this may reduce hepatic blood flow. Lumbar thoracic anesthesia is shown to reduce liver blood flow in nonhuman and human studies [2]. Patients undergoing major abdominal surgery, such as hepatectomy, are at risk for postoperative complications, including multiple organ failure. Epidural anesthesia and

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Table 1. Patient Demographics and Characteristics

Variable	Group I ($n = 20$)	Group II ($n = 20$)	*P* Value
Age (y)	27.5 ± 7.5	26.5 ± 7.8	.523
Sex (M/W)	16/4	12/8	.399
Height (cm)	172.1 ± 7.5	169.2 ± 8.2	.802
ASA I/II (*n*)	5/15	14/6	.245
Weight (kg)	69.9 ± 8.9	69.1 ± 7.8	.696

Note. Values are presented as mean ± SD or *n*. Group I: control; group II: epidural.

Abbreviation: ASA, American Society of Anesthesiologists physical status.

analgesia are shown to be effective in reducing perioperative risks, such as intraoperative blood flow and thromboembolic events, and improving postoperative respiration, cardiovascular, and intestinal function and modified immune function. In addition, epidural anesthesia is considered to increase organ perfusion in the splenic area by means of sympathetic blockage [3].

Indocyanine green test (ICG) was initially designed to measure blood flow and then started to be used to assess liver function by means of measuring functional hepatocyte mass. The most frequently used test in clinical practice is numeric liver function test. ICG clearance test is indicated in the assessment and monitoring of liver functions in the liver transplant recipients and donors [4].

Our goal of the present study was to compare the efficacy of thoracic epidural anesthesia (TEA) compared with general anesthesia with the use of ICG and liver function tests.

METHODS

This study was performed from January to September 2013 on 40 patients aged 18–55 years in American Society of Anesthesiologists (ASA) physical status I-II who had undergone general anesthesia for liver transplant right hepatectomy at the Department of Anesthesiology and Reanimation, Faculty of Medicine, Inonu University, after the consents of the Malatya Clinical Research Ethical Board (2013/46) and of the patients were obtained. Patients' sex, age, height, smoking, body weight, body mass index, and ASA physical status were recorded. The patients were divided into 2 equal groups: the control group (group I) and the epidural block group (group II, closed envelope method). In the operating room, electrocardiography, oxygen saturation, and noninvasive blood pressure monitoring were performed and basal hemodynamic values recorded. Bispectral index (BIS) was used to assess depth of anesthesia. In group 2 patients, the epidural catheter was inserted at the $T_{6\text{-}8}$ level. In all patients, anesthesia was standardized with lidocaine, fentanyl, and thiopental. Patients were intubated after muscle relaxation provided with the use of vecuronium. Anesthesia maintenance, in 50/50% oxygen-air mixture, in group 1 consisted of isoflurane, remifentanil infusion, and cisatracurium infusion, and in group 2 patients isoflurane, epidural infusion, and cisatracurium infusion. Nondominant radial artery invasive arterial blood pressure monitoring was provided. An internal jugular venous catheter was inserted for central venous pressure monitoring in all patients. Patients' mean arterial pressure, heart rate, pulse oximetry, and BIS values were recorded. Pringle maneuver time (if applied), remnant liver, total amount of bleeding, amount of urine, total anesthesia time, total operation time, times of operation phases, total amount of liquid during operation, and type of fluid (crystalloid, colloid, blood, and blood products) were recorded. After transection, the graft weight was also recorded. After antagonizing the effects of muscle relaxants at the end of the operations, patients were extubated. After observed in the postoperative care unit for one-half hour, patients were sent to the surgical intensive care unit. ICG clearance test values before general anesthesia (T0), after induction of general anesthesia (T1), after transection (T2), and at postoperative 24 and 72 hours (T3 and T4) were recorded. Simultaneously, hemoglobin, hematocrit, platelet count, prothrombin time (PT), international normalized ratio (INR), total bilirubin, direct bilirubin, albumin, aspartate transaminase, and alanine transaminase (ALT) values were analyzed.

Statistical Analyses

The SPSS 16.0 package program was used in the statistical analyses of the data. With the use of Kolmogorov-Smirnov normality test, data belonging to quantitative variables were determined to show normal distribution ($P > .05$). Paired *t* test was used to test the change in data during the course of time. Independent *t* test was used in the intergroup comparisons. Data belonging to quantitative variables are presented as mean ± SD, and data belonging to qualitative variables are presented as *n* (%). $P < .05$ was considered to be statistically significant.

Table 2. Average Values of the Groups and Intergroup Comparisons of Duration of Operation, Urine, Temperature, Remnant Liver, Graft Weight, and Bleeding Volume

Variable	Group I ($n = 20$)	Group II ($n = 20$)	*P* Value
Duration of anesthesia (min)	396 ± 83	353 ± 71	.393
Duration of surgery (min)	345 ± 80	305 ± 74	.921
Urine output (mL)	1,086 ± 477	1,062 ± 497	.878
Temperature (°C)	36.8 ± 0.7	36.6 ± 0.7	.784
Remnant liver (%)	32 ± 5	33 ± 4	.883
Bleeding volume (mL)	298 ± 75	330 ± 114	.006
Graft weight (g)	773 ± 142	734 ± 108	.379

Note. Values are presented as mean ± SD or *n*. Group I: control; group II: epidural.

RESULTS

Demographic properties of the patients are presented in Table 1. In terms of operation time, percentage of liver remnant, graft weight and amount of bleeding, statistically significant difference was not observed between groups (Table 2). Significant changes in the ALT levels were observed over time within both groups ($P < .05$), but there no significant difference between groups. PT and INR values were significantly different over time within both groups ($P < .05$, Table 3). Regarding SAP, MAP and CVP values were significantly different over time within both groups ($P < .05$, Table 4). Regarding PDR and R15 of ICG, statistically significant difference was not observed between groups ($P > .05$). In intragroup comparisons of PDR and R15 values at T1, T2, T3, and T4, the values at T0 were statistically significant in both groups ($P < .05$, Table 5).

Table 3. Laboratory Values of the Groups

	T0	T1	T2	T3	T4
Hemoglobin					
Group I	15.1 ± 1.9	13.9 ± 2.1*	13.6 ± 2.4*	14.1 ± 2.1*	13.5 ± 2.2*
Group II	14.4 ± 1.7†	13.3 ± 1.6*	12.4 ± 1.7*	13.6 ± 1.7*	12.4 ± 1.3*,†
Hematocrit					
Group I	44.1 ± 4.9	40.6 ± 5*	39.5 ± 5.5*	40.1 ± 5.3*	39.3 ± 6.2*
Group II	43.1 ± 4.8†	39.6 ± 4.7*	36.7 ± 5.2*	38.8 ± 4.6*	36.1 ± 3.1*,†
Thrombocyte					
Group I	259 ± 60	232 ± 59*	226 ± 45*	216 ± 42*	197 ± 42*
Group II	267 ± 59	254 ± 71*	246 ± 67*	223 ± 69*	195 ± 59*
Prothrombin time					
Group I	13.6 ± 1.2	13.9 ± 1.3	14.9 ± 1.8*	21.4 ± 3.7*	18.5 ± 2.6*,†
Group II	13.3 ± 0.6	13.8 ± 0.9*	16.1 ± 5.5*	19.8 ± 6.7*	16.9 ± 1.5*
International normalized ratio					
Group I	1.05 ± 0.11	1.1 ± 0.11*	1.2 ± 0.16*	1.9 ± 0.37*	1.5 ± 0.23*,†
Group II	1 ± 0.06	1.1 ± 0.13	1.3 ± 0.66*	1.8 ± 0.65*	1.4 ± 0.15*
Albumin					
Group I	4.2 ± 0.3	4.2 ± 0.3	3.2 ± 0.4*	3.2 ± 0.3*	3.2 ± 0.3*
Group II	4.2 ± 0.2	4.2 ± 0.2	2.9 ± 0.4*	3.2 ± 0.5*	3.2 ± 0.2*
Total bilirubin					
Group I	0.5 ± 0.3	0.7 ± 0.3*	1 ± 0.4*	2.7 ± 1.8*	3.1 ± 2.4*
Group II	0.6 ± 0.4	0.7 ± 0.4*	1 ± 0.5*	2.6 ± 1.1*	2.3 ± 1.3*
Direct bilirubin					
Group I	0.2 ± 0.1	0.3 ± 0.1*	0.5 ± 0.2*	0.8 ± 0.7*	1.5 ± 1.3*
Group II	0.2 ± 0.1	0.3 ± 0.1*	0.4 ± 0.2*	0.8 ± 0.3*	1 ± 0.6*
Aspartate transaminase					
Group I	19 ± 4.5	36 ± 26	132 ± 87*	206 ± 78*	109 ± 39*
Group II	18 ± 3.7	35 ± 36	117 ± 43*	193 ± 95*	86 ± 22*,†
Alanine transaminase					
Group I	19 ± 11	39 ± 35	121 ± 87*	213 ± 107*	140 ± 75*
Group II	18 ± 6	34 ± 38	111 ± 43*	216 ± 118*	125 ± 49*

Note. Values are presented as mean ± SD or *n*. Group I: control; group II: epidural.
*Difference from T0 ($P < .05$).
†Intergroup difference ($P < .05$).

DISCUSSION

In this study, we determined that TEA does not affect ICG clearance in liver transplant donors. We observed that PDR and R15 values are similar with patients undergoing general anesthesia and those undergoing TEA. However, this study demonstrated that time for PT, INR, and ALT values to reach normal levels was shorter and that hemodynamic stability was better maitained in patients undergoing TEA.

Hepatic blood flow is affected by arterial blood flow, posture changes, $PaCO_2$ level, intravascular fluid changes, ventilation with positive pressure, and volatile anesthetics in surgery patients [5]. Trepenaitis et al [2] reported that hepatic blood flow showed predictable decrease compared with basal measurement values of hepatic blood flow in patients under general anesthesia and receiving mechanic ventilation. Whether TEA lowers perioperative risk or not has been discussed for a long time. Although TEA is a frequently used technique, limiting the effect on hepatic blood flow from blockage of thoracic segments is not clearly studied. TEA affects sympathetic thoracic pathways and may lead to regional arteriolar dilatation and increase in regional blood flow. On the other hand, systemic hypotension develops as a result of decrease in the hepatic blood flow with decreasing systemic vascular resistance. Lumbar epidural anesthesia is shown to reduce hepatic blood flow in nonhuman and human studies [6–9]. However, Vagts et al [10] demonstrated that TEA, which they performed in a nonhuman animal model, did not result in change in hepatic blood flow despite reducing systemic arterial blood flow. In addition, all measurements were started before the surgical processes and fluid administration continued throughout the study. Thus, measurements were performed hemodynamically at stable heart rate and blood pressure levels.

Table 4. Intergroup Hemodynamic Data

Variable	Group I ($n = 20$)	Group II ($n = 20$)	*P* Value
HR (beats/min)	84 ± 10	88 ± 9	.193
SAP (mm Hg)	116 ± 10	104 ± 7	.000
DAP (mm Hg)	68 ± 7	66 ± 5	.050
MAP (mm Hg)	84 ± 9	78 ± 5	.011
CVP (mm Hg)	3.8 ± 2.6	6.1 ± 2.9	.016

Note. Values are presented as mean ± SD or *n*. Group I: control; group II: epidural.
Abbreviations: HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure.

Table 5. Average Values of Groups According to ICG Clearance Test Measurements Over Time

	T0	T1	T2	T3	T4
Plasma disappearance rate					
Group I	32 ± 6.8	21.7 ± 6.2*	15.5 ± 4.6*	14.7 ± 4.8*	15.6 ± 5.3*
Group II	30 ± 6.4	20 ± 7.2*	14.5 ± 2.8*	13.1 ± 2.4*	15.5 ± 3.2*
Retention at 15 minutes					
Group I	1.1 ± 0.8	6.3 ± 7.6*	11.5 ± 6.7*	14 ± 10.1*	13.3 ± 11.4*
Group II	1.7 ± 1.9	9.1 ± 13.3*	12.3 ± 4.4*	14.8 ± 5.4*	10.8 ± 5.7*

Note. Values are presented as mean ± SD or *n*. Group I: control; group II: epidural.
*Difference from T0 ($P < .05$).

Similarly in our study, we determined that ICG clearance tests, PDR and R15 values, were not influenced by the application of TEA.

ICG clearance test is considered to be an important marker in the detection of regional hepatic perfusion. There is only 1 nonhuman study and 2 human studies demonstrating the effect of TEA on hepatic blood flow at present. Similarly to the results of our study, Vagts et al [10] demonstrated nearly 30% decrease in mean arterial pressure without influencing total hepatic blood flow in a pig model after the application of TEA ($T_{5\text{-}12}$ level). This result leads to the consideration that similar blood flow and hemodynamic data are obtained in humans as a result of similar sympatholysis. However, Kortgen et al [3] demonstrated, contrary to our study, that TEA increased hepatic perfusion in most patients after major abdominal surgery. Meierhenrich et al [11] reported that TEA along with transesophageal echocardiography significantly decreased hepatic venous blood flow. However, in that study, results were obtained with the use of norepinephrine infusion in addition to TEA application. The effect of high-lumbar epidural anesthesia on hepatic blood flow was evaluated in 3 human studies. Kennedy et al [8] reported that hepatic blood flow is decreased to 25% in healthy volunteers despite constant cardiac flow. Tanaka et al [9] reported that high-lumbar epidural anesthesia decreased hepatic blood flow by 35% according to measurement of PDR and ICG clearance. Simon et al [12] showed that hepatic blood flow decreased after lumbar epidural anesthesia according to the pulse densitometric noninvasive method and ICG clearance measurement. In the present study, we have shown that hepatic blood flow did not change according to ICG clearance tests, ie, PDR and R15 criteria, after the application of TEA.

As a consequence, we think that TEA applied in elective liver donor patients does not affect the ICG clearance test which is used in the assessment of global liver function test nor other routine tests related to the liver.

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