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Research Article

Monoethylglycinexylidide extraction level as a measure of hepatic detoxification and excretion functions in cirrhotics undergoing laparoscopic cholecystectomy under general anesthesia

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KEYWORDS

Cirrhotic patients;
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Abstract *Objectives:* To estimate plasma monoethylglycinexylidide (MEGX) level at 15 and 30 min after intravenous injection of lidocaine as a measure for detoxification and excretory function of the liver in cirrhotic patients in comparison with non-cirrhotic patients assigned for laparoscopic cholecystectomy (LC).

Patients and methods: The study included 50 cirrhotic and 10 non-cirrhotic patients assigned for LC. Only Child-Pugh (CP) class A or B patients with adjusted liver functions were included in the study. Both patients and controls received anesthesia using a similar protocol. Intravenous lidocaine (1 mg/kg) was injected over 1 min, and blood samples were obtained immediately before lidocaine injection (S_0) to assure absence of MEGX in plasma and 15 min (S_{15}) and 30 min (S_{30}) after lidocaine administration. MEGX values > 90 ng/ml are considered normal. The extent of MEGX extraction was calculated as plasma MEGX level at S_{30} minus S_{15}.

Results: Mean operative and anesthesia times were 59.3 ± 10.4 and 73.9 ± 12.2 min, respectively. Mean sevoflurane 18.1 ± 2.4 ml/h. Operative and anesthetic data showed non-significant difference between patients categorized according to CP class and in comparison with controls. Estimated plasma MEGX levels at 15-min and 30-min after lidocaine injection were significantly higher in controls compared to patients and in patients of CP class A compared to those of class B. The

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extent of extraction was significantly lower in patients of CP class B compared both to controls and patients of class A with non-significantly lower extraction level in patients of class A compared to controls.

Conclusion: Laparoscopic cholecystectomy is safe and feasible in cirrhotic patients and MEGX test as a measure of detoxification and excretory function of the liver is a reliable test that showed a relationship to the extent of hepatic derangement.

1. Introduction

Cirrhosis causes a hyperdynamic circulation with increased cardiac output and decreased systemic vascular resistance; however, it endangers hepatic circulation in the form of decreased venous perfusion secondary to reduced portal blood flow as a consequence of portal hypertension. Also, hepatic arterial blood flow can be decreased because of impaired autoregulation [1,2].

The burden of operative risk on the liver is dependent on both the underlying liver disease, type of surgery, operative approach, and duration. Anesthetics increase the burden on hepatic blood flow in the form of reduced hepatic blood flow by 30–50%, but agents such as isoflurane, desflurane, sevoflurane, and propofol cause less perturbation in hepatic arterial blood flow than other inhaled anesthetic agents and so are preferred for patients with liver disease. Traction on abdominal viscera may cause reflex dilatation of splanchnic veins and thereby lower hepatic blood flow [3–5].

Dynamic tests are related to the ability of the liver to metabolize or eliminate defined substances in a given time. Thus, dynamic tests have the advantage of quantifying the functional status at the time point of assessment. Historically, the bromosulfophthalein and indocyanine green tests have been used as dynamic function tests. Unfortunately, these tests are no longer used because of lack of commercial availability of bromosulophthalein and high cost of indocyanine green [6,7].

Lignocaine is a compound with a high hepatic extraction and an oxidative metabolic pathway catalyzed by the hepatic P450 IIIA4 cytochrome yielding monoethylglycinexylidide (MEGX). Estimation of plasma MEGX levels after intravenous injection of lignocaine constitutes a simple dynamic liver function test. The idea behind this test is to detect reduced clearance of lidocaine in cases of liver diseases or reduced hepatic blood flow by measurement of plasma MEGX. Reduced liver function or hepatic blood flow results in reduced formation of MEGX in humans. This test has the advantage that it is easy to do [7,8].

The current prospective study aimed to estimate plasma MEGX level at 15 and 30 min after intravenous injection of lidocaine as a measure for detoxification and excretory function of the liver in cirrhotic patients in comparison with control non-cirrhotic patients assigned for laparoscopic cholecystectomy.

2. Patients and methods

The current prospective comparative study was conducted at Anesthesia Department, Kasr Al-Eini University Hospital since Jan 2009 till June 2012. After approval of the study protocol by the Local Ethical Committee and obtaining fully informed written patients' consent, 50 cirrhotic patients assigned for laparoscopic cholecystectomy (LC) were enrolled in the study. For comparative purposes, 10 non-cirrhotic, age-, and sex-matched controls assigned for LC were enrolled in the study.

Inclusion criteria included cirrhotic patients whose hospital files included the required preoperative data especially liver function tests, abdominal ultrasonography, and their baseline Child-Pugh (CP) class. Only patients with adjusted liver functions and were CP class A or B were included in the study. Patients with clinically detectable ascites or had history of or defined obstructive jaundice or recent attack of gastrointestinal bleeding were excluded from the study. Both study and control groups received anesthesia using a similar protocol. Atropine 0.2 mg and midazolam 0.03 mg/kg were administered IV before induction of anesthesia. Anesthesia was induced with fentanyl 1–2 μg/kg and propofol 2 mg/kg Endotracheal intubation was facilitated by IV atracurium 0.5 mg/kg. Anesthesia was maintained with sevoflurane in oxygen 3 l/min. Ventilation was controlled to keep PaCO2 between 30 and 40 mmHg. Atracurium was used as a muscle relaxant during surgery. Non-invasive intraoperative monitoring included heart rate (HR), systolic, and diastolic blood pressure (SBP & DBP). After surgery, all patients were extubated and were followed in ICU for 24 h and thereafter in the surgical ward. At ICU, heart rate, blood pressure, and oxygen saturation were monitored continuously with a non-invasive method.

2.1. Estimation of serum MEGX

All samples were taken from a plastic cannula on the contralateral arm to that used for the administration of lidocaine. The cannula was kept patent with a trocar. Blood samples were drawn into EDTA; plasma was separated within 30 min and stored at −40 °C until analysis. Concentrations of monoethylglycinexylidide (MEGX) were analyzed with gas chromatography using etidocaine as an internal standard [9].

Intravenous lidocaine was injected in a sub-therapeutic dose (1 mg/kg) over 1 min after transfer to ICU. Blood samples were obtained immediately before lidocaine injection (S_0) to assure absence of MEGX in plasma and 15 min (S_{15}) and 30 min (S_{30}) after lidocaine administration. MEGX values > 90 ng/ml are considered normal, whereas values below 50 ng/ml reflect impaired liver function and values ranged between 50 and 90 ng/ml reflect affected liver function [9]. The extent of MEGX produced as a measure for detoxification and excretion functions of the liver was calculated as plasma MEGX level at S_{30} minus S_{15}.

2.2. Statistical analysis

Results were presented as mean ± SD, ranges, numbers, percentages, and ratios. Data were analyzed using Chi-square test

(X^2 test) for numbers and percentages and Wilcoxon Ranked test for unrelated data for inter-group comparisons. Statistical analyses were conducted using SPSS (Version 15, 2006) program, and p value < 0.05 was considered significant.

3. Results

The study included 50 cirrhotic patients; 16 males and 34 females with mean age of 45.4 ± 7.3; range: 33–55 years and 10 controls; 4 males and 6 females with mean age of 45.3 ± 7.2; range: 35–54 years. There were 29 CP class A patients and 21 CP class B patients. There was non-significant ($p > 0.05$) difference between patients and controls and among patients categorized according to CP class as regards age and gender distribution.

Mean operative time was 59.3 ± 10.4; range: 40–75 min for patients and was 60.5 ± 6.9; range: 50–70 min for controls. Mean anesthesia time was 73.9 ± 12.2; range: 53–95 min for patients and was 74.1 ± 10; range: 60–88 min for controls. Mean sevoflurane consumption was 18.1 ± 2.4; range: 14–22 ml/h, while for controls was 18.4 ± 2.5; range: 15–22 ml/h. Operative and anesthetic data showed non-significant ($p > 0.05$) difference between patients categorized according to CP class and in comparison with controls (Table 1).

All patients and controls showed significantly higher heart rate and blood pressure measures after insufflation compared to both baseline and post-desufflation measures with non-significantly higher measures after desufflation in comparison with baseline measures. However, these hemodynamic responses were similar in both studied groups with non-significant difference between patients categorized according to CP class and between both patients' groups and controls (Table 2).

Estimated plasma MEGX levels at 15-min and 30-min after lidocaine injection were significantly higher in controls compared to patients categorized according to CP class with significantly higher plasma MEGX levels in patients of CP class A compared to those of class B. The extent of extraction was significantly lower in patients of CP class B compared both to controls and patients of class A with non-significantly lower extraction level in patients of class A compared to controls (Table 3).

4. Discussion

The applicability of routine liver tests could not predict the anesthetic and surgical burden on liver; considering the ability of liver for extraction and detoxification of certain substance and excretion of its non-toxic metabolites either in biliary passages or blood sinusoids is one of the major functions of the liver and reflects its affection by pre-existing diseases or by risk-exposure [10–12]. MGEX is the major metabolism product of lidocaine and considering lidocaine as a substance not normally synthesized in the body, and subsequently, its metabolites are not present in circulation, so its estimation could reflect the detoxification and extraction function of the liver [8,13].

All patients and controls showed affection by surgical and anesthetic effect as manifested by the finding that none of patients had 30-min plasma MGEX level ⩾90 ng/ml; while only 3 of control had 30-min plasma MGEX of >90 ng/ml. This affection could be attributed to the effect imposed by pneumoperitoneum on hepatic blood flow and subsequent liver abilities and functions. In support of this assumption, Nickkholgh et al. [14] experimentally reported that increase in intraabdominal pressure (IAP) to 12 mmHg significantly increased liver enzymes measured after desufflation to almost 1.5 times as much as control values and in parallel, in all subacinar zones the permanent adherence of both leukocytes and platelets to the endothelium increased by about sixfold and threefold, respectively, also. Kupffer cells labeled with latex beads as an index for their activation were significantly increased compared to controls. Also, Eiriksson et al. [15] experimentally compared raised IAP during laparoscopic hepatectomy to 8 or 16 mmHg and found high IAP reduces the amount of bleeding. Sánchez-Etayo et al. [16] experimentally reported that total liver blood flow remained mostly unaltered at low IAP, but as IAP increased, a significant decline in hepatic microcirculatory blood flow was observed.

The current study found that the excretory function of liver was maintained in both classes of cirrhosis as manifested by increased plasma levels of MEGX at 30-min in comparison with levels estimated at 15-min. However, patients of class A had more preserved excretory function compared to those of class B as manifested by a significantly higher extent of excretion in patients of class A compared to patients of class B. These data indicated a negative relationship between the CP class as a reflection of liver derangement and plasma MEGX level and so it could be used as a marker for deterioration of liver function and prediction of outcome.

In line with these findings, Sakka [17] found MEGX for lidocaine metabolism as an available dynamic test that may be recommended in critically ill patients for assessing liver

Table 1 Operative and anesthetic data.

	Control ($n = 10$)	CP class A ($n = 29$)	CP class B ($n = 21$)	Statistical significance
Operative time (min)	60.5 ± 6.9 (50–70)	59.9 ± 9.3 (43–75)	58.5 ± 12 (40–75)	$Z = 0.283$; $p_1 > 0.05$ $Z = 0.577$; $p_2 > 0.05$ $Z = 0.179$; $p_3 > 0.05$
Anesthesia time (min)	74.1 ± 10 (60–88)	72.6 ± 10 (55–89)	75.7 ± 15 (53–95)	$Z = 0.400$; $p_1 > 0.05$ $Z = 0.562$; $p_2 > 0.05$ $Z = 1.231$; $p_3 > 0.05$
Sevoflurane consumption (ml/h)	18.4 ± 2.5 (15–22)	18 ± 2.4 (14–22)	18.2 ± 2.4 (15–22)	$Z = 1.646$; $p_1 > 0.05$ $Z = 0.604$; $p_2 > 0.05$ $Z = 1.547$; $p_3 > 0.05$

Data are presented as mean ± SD & ranges are in parenthesis; p_1: significance between CP class A and controls; p_2: significance between CP class B and controls; p_3: significance between CP class A and CP class B patients.

Table 2 Hemodynamic data of studied patients recorded after peritoneal insufflation and desufflation compared to baseline data.

		Baseline	Post-insufflation	Post-desufflation	
HR (beats/min)	Controls ($n = 10$)	78.1 ± 4.9	86.9 ± 4.3	82.5 ± 3.5	$Z = 2.670$; $p_4 = 0.008$ $Z = 1.330$; $p_5 > 0.05$ $Z = 2.251$; $p_6 = 0.024$
	CP class A ($n = 29$)	77.7 ± 3.7	85.5 ± 5.4	81.8 ± 3.9	$Z = 2.706$; $p_4 = 0.007$ $Z = 1.481$; $p_5 > 0.05$ $Z = 2.814$; $p_6 = 0.024$
	CP class B ($n = 21$)	80.7 ± 4.7	85.3 ± 4.7	81.7 ± 5.5	$Z = 2.048$; $p_4 = 0.041$ $Z = 0.309$; $p_5 > 0.05$ $Z = 3.173$; $p_6 = 0.019$
	Statistical significance	$Z = 1.693$; $p_1 > 0.05$ $Z = 0.707$; $p_2 > 0.05$ $Z = 1.228$; $p_3 > 0.05$	$Z = 0.357$; $p_1 > 0.05$ $Z = 1.842$; $p_2 > 0.05$ $Z = 0.892$; $p_3 > 0.05$	$Z = 1.330$; $p_1 > 0.05$ $Z = 1.227$; $p_2 > 0.05$ $Z = 0.579$; $p_3 > 0.05$	
SBP (mmHg)	Controls ($n = 10$)	118 ± 8.5	125.3 ± 3	122.2 ± 3	$Z = 2.314$; $p_4 = 0.021$ $Z = 1.376$; $p_5 > 0.05$ $Z = 2.652$; $p_6 = 0.008$
	CP class A ($n = 29$)	120 ± 4.5	125.3 ± 3.3	123.9 ± 4.5	$Z = 3.555$; $p_4 < 0.001$ $Z = 3.531$; $p_5 > 0.01$ $Z = 2.922$; $p_6 = 0.023$
	CP class B ($n = 21$)	119 ± 4	124.1 ± 3.6	122.8 ± 4.2	$Z = 3.377$; $p_4 = 0.001$ $Z = 2.818$; $p_5 > 0.05$ $Z = 2.438$; $p_6 = 0.024$
	Statistical significance	$Z = 2.023$; $p_1 > 0.05$ $Z = 1.226$; $p_2 > 0.05$ $Z = 1.125$; $p_3 > 0.05$	$Z = 1.027$; $p_1 > 0.05$ $Z = 0.793$; $p_2 > 0.05$ $Z = 0.457$; $p_3 > 0.05$	$Z = 1.756$; $p_1 > 0.05$ $Z = 1.989$; $p_2 > 0.05$ $Z = 0.789$; $p_3 > 0.05$	
DBP (mmHg)	Controls ($n = 10$)	74.5 ± 3	79.6 ± 3.6	77.7 ± 6.9	$Z = 2.670$; $p_4 = 0.008$ $Z = 1.330$; $p_5 > 0.05$ $Z = 2.251$; $p_6 = 0.024$
	CP class A ($n = 29$)	73.8 ± 2.3	80 ± 4.9	76.8 ± 4.5	$Z = 2.706$; $p_4 = 0.007$ $Z = 1.481$; $p_5 > 0.05$ $Z = 2.814$; $p_6 = 0.024$
	C*P* class B ($n = 21$)	74.7 ± 3.4	79.9 ± 6.5	77.1 ± 5.2	$Z = 2.048$; $p_4 = 0.041$ $Z = 0.309$; $p_5 > 0.05$ $Z = 2.473$; $p_6 = 0.024$
	Statistical significance	$Z = 1.693$; $p_1 > 0.05$ $Z = 0.707$; $p_2 > 0.05$ $Z = 1.228$; $p_3 > 0.05$	$Z = 0.357$; $p_1 > 0.05$ $Z = 1.842$; $p_2 > 0.05$ $Z = 0.892$; $p_3 > 0.05$	$Z = 1.330$; $p_1 > 0.05$ $Z = 1.227$; $p_2 > 0.05$ $Z = 0.579$; $p_3 > 0.05$	

Data are presented as mean ± SD; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; p_1: significance between CP class A and controls; p_2: significance between CP class B and controls; p_3: significance between CP class A and CP class B patients; p_4: significance between baseline and post-insufflation levels; p_5: significance between baseline and post-desufflation levels; p_6: significance between post-insufflation and post-desufflation levels.

Table 3 Plasma MEGX levels estimated at 15-min and 30-min after lidocaine injection.

	15-min level	30-min level		Extent of extraction
Controls ($n = 10$)	77.6 ± 5.4 (65–84)	85.3 ± 5.3 (75–83)	$Z = 2.809$; $p_4 = 0.005$	7.7 ± 2.2 (5–11)
CP class A ($n = 29$)	65.3 ± 5.8 (50–78)	70.9 ± 5.5 (54–83)	$Z = 4.041$; $p_4 > 0.001$	5.7 ± 1.7 (2–8)
CP class B ($n = 21$)	41 ± 6.8 (31–56)	45.4 ± 6 (37–59)	$Z = 4.723$; $p_4 > 0.001$	4.4 ± 1.6 (2–7)
Statistical significance	$Z = 2.812$; $p_1 = 0.005$ $Z = 4.018$; $p_2 < 0.001$ $Z = 2.397$; $p_3 = 0.017$	$Z = 2.807$; $p_1 = 0.005$ $Z = 4.016$; $p_2 < 0.001$ $Z = 2.603$; $p_3 = 0.009$		$Z = 1.672$; $p_1 > 0.05$ $Z = 2.814$; $p_2 = 0.005$ $Z = 2.089$; $p_3 = 0.007$

Data are presented as mean ± SD; p_1: significance between CP class A and controls; p_2: significance between CP class B and controls; p_3: significance between CP class A and CP class B patients; p_4: significance between 15-min and 30-min levels.

function, liver blood flow, and cell function. Also, Bhise and Dias [18] reported that MEGX test is more discriminatory and recognizes early damage to the liver than conventional individual liver function tests. Hofmann et al. [19] reported that dynamic tests as indocyanine green clearance and MEGX clearance tests can provide additional information on the expected residual hepatic function in patients with CP class A cirrhosis. Pérez-Guillé et al. [20] experimentally suggested that

the ratio of MEGX/lidocaine obtained 30 min after lidocaine administration could be a good marker of hepatic metabolic function.

In line with the applicability of MEGX test for prediction of patient's outcome, Botta et al. [21] found MEGX serum levels were significantly different among patients who survived and those who died and were independently associated with six month mortality. Lorf et al. [22] found that MEGX-test, especially the 30 min value, is a useful medium to estimate the liver reserve in non-cirrhotic patients prior to liver resection, and in combination with the resection volume, it may be very useful to identify patients with a high risk of developing a postoperative liver failure. Laviolle et al. [23] assessed liver function recovery after partial hepatectomy using MEGX plasma level estimated 15 min after lidocaine injection on day 2 after surgery and found that estimation of MEGX correlate with liver function outcome.

In support of the correlation between plasma MEGX and extent of liver injury, Ben Said et al. [24] developed an ex vivo functional assay to assess liver metabolic capacity adapted from the lidocaine test in rats and found that both lidocaine metabolism and MEGX formation levels were significantly altered in all models of hepatic injury and the extent of hepatic damage was confirmed by increased trans-aminase levels and alteration of hepatocyte's structure with areas of necrosis.

5. Conclusion

It could be concluded that laparoscopic cholecystectomy under general inhalational anesthesia is safe and feasible in cirrhotic patients and MEGX test as a measure of liver detoxification and excretory function is a reliable test that showed a relationship to the extent of hepatic derangement.

Conflict of Interest

The authors declare that there are no conflict of interest.

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