Intraoperative estimation of serum MEGX as a prognostic parameter in cirrhotic patients undergoing laparoscopic Surgery under Sevoflurane anaesthesia

Wael ahmed Ibrahim[1]; Ahmed abdalla Mohamed[2] and Tamer Fayez safan[2]

[1] Anaesthesia Department, NCI Cairo University
[2] Anaesthesia Department, Faculty of Medicine Cairo University
waelahmed60@yahoo.com

Abstract: Objectives: To evaluate the applicability of serum mono-ethyl-glycine-xylidide (MGEX) estimation as a prognostic parameter in cirrhotic patients exposed to inhalational anesthesia for varied laparoscopic surgeries. **Patients & Methods:** The study included 30 cirrhotic patients and 10 controls non-cirrhotic patients assigned to undergo surgical procedures under general inhalational anesthesia. Preoperative evaluation included clinical, ultrasonographic examination and laboratory investigations for the patients, and they are categorized according to Child-Pugh (CP) score. Only patients with CP class A and B were enrolled in the study. Serum MEGX was estimated 15 and 30 minutes after intravenous injection of lidocaine 1 mg/kg over 1 min. The amount of MEGX produced as a measure for detoxification and excretion liver functions was calculated as serum MEGX level at 30 minutes (S_{30}) minus serum MEGX at 15 minutes (S_{15}). **Results:** Nineteen patients were CP class A and 11 were class B. Mean operative and anesthesia times showed non-significant difference between studied patients. Mean sevoflurane consumption was 310±30.9 MAC/hr with a non-significant difference between studied patients. All patients developed significantly higher heart rate and blood pressure measures at time of abdominal insufflations compared to baseline but returned to near baseline levels after exsufflation. Serum MEGX was non-significantly higher in S_{30} sample compared to S_{15} sample. No patient approached the level of ≥90 ng/ml. Patients of CP class B showed significantly lower serum levels of MEGX in both samples compared to CP class A patients. The extent of increase of MEGX serum levels showed a negative significant correlation with occurrence of postoperative deterioration of CP class and postoperative morbidities that ended fatally in two patients. **Conclusion:** Estimation of serum MEGX is applicable and could be used as discriminative test for patients with varied degrees of liver cirrhosis and as predictor for prognosis after exposure to anesthetic and surgical risks.

[Wael ahmed Ibrahim; Ahmed abdalla Mohamed and Tamer Fayez safan. **Intraoperative estimation of serum MEGX as a prognostic parameter in cirrhotic patients undergoing laparoscopic Surgery under Sevoflurane anaesthesia.** *J Am Sci* 2012;8(7):575-580]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 88

Keywords: Cirrhosis, Inhalational anesthesia, Laparoscopic surgery, MEGX

1. Introduction

Hepatic operative risk is definite but unrelated to type of anesthetic maneuver applied. Minor postoperative elevation of serum liver function markers in patients without underlying liver disease are not clinically significant; however, in patients with underlying liver diseases especially if hepatic synthetic function was compromised, such risk is manifest. The burden of operative risk on the liver is dependent on both the underlying liver disease, type of surgery, operative approach and duration [1, 2].

Despite cirrhosis causes a hyperdynamic circulation with increased cardiac output and decreased systemic vascular resistance, 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 [3].

Anesthetics and surgical procedures increase the burden on hepatic blood flow; anesthetic agents may reduce 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 [4, 5].

Risk factors for acute intraoperative hypoxemia in patients with cirrhosis include ascites, hepatic hydrothorax, hepatopulmonary syndrome which is the triad of liver disease, an increased alveolar-arterial gradient and intrapulmonary shunting which is found in 5–32% of cirrhotic patients followed at transplant centers, and porto-pulmonary hypertension, which is found in up to 6% of patients with advanced liver disease and which increases postoperative mortality after non-cardiac surgery [6, 7]. Thus, preoperative clinical assessment of the severity of liver disease is mandatory; the severity of liver disease can best be assessed by the Child-Turcotte-

Pugh (CTP) score, Child-Pugh class and the Model for End-Stage Liver Disease (MELD) score [8].

Lignocaine is a flow-dependent xenobiotic compound with a high hepatic extraction and an oxidative metabolic pathway catalyzed by the hepatic P450 IIIA4 cytochrome yielding mono-ethyl-glycine-xylidide (MEGX). Estimation of serum MEGX levels after intravenous injection of lignocaine constitutes a simple dynamic liver function test [9]. This prospective study aimed to evaluate the reliability of estimation of serum MGEX level as a prognostic parameter for hepatic derangement in cirrhotic patients exposed to inhalational anesthesia during varied types of laparoscopic surgeries.

2. Patients & Methods

The present study was conducted at Anesthesia Department, Kasr Al-eni university hospital in the period from Jan 2011 up to Dec 2011 and designed to include 30 cirrhotic patients assigned for laparoscopic general surgical procedures under general anesthesia. The study also included 10 non-cirrhotic age and sex-matched patients assigned to undergo laparoscopic general surgical procedures under general anesthesia as control group. Written informed consent was obtained from all patients.

Preoperative evaluation included clinical and ultrasonographic examination for evaluation of the grade of cirrhosis. Preoperative laboratory investigations included estimation of serum albumin and total bilirubin levels and determination of the international normalized ratio (INR) for prothrombin. Then patients were categorized according to Child-Pugh score [10], into 3 classes A: 5-6 points, B: 7-9 points and C: 10-15 points according to criteria shown in table 1. All patients were admitted at Internal Medicine wards for preoperative adjustment of liver functions so as to be ready for surgery. Only patients with Child class A and B were enrolled in 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 anaesthesia. Anesthesia was induced with fentanyl 1-2 µg/kg and propofol 2 mg/kg Endotracheal intubation was facilitated by IV pancuronium 0.08 mg/kg. Anesthesia was maintained with sevoflurane with oxygen 3 L/min. Ventilation was controlled to keep $PaCO_2$ between 30 and 40 mm Hg. Pancuronium 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 tracheally extubated and were followed up in ICU for 24 hours and thereafter in the surgical ward. At ICU, heart rate, blood pressure and oxygen saturation were monitored continuously with a noninvasive method.

Table (1): Criteria and score points for calculation of Child-Pugh score [10]

Score (points) Criteria	1	2	3
Serum total bilirubin	<2 mg/dl	2-3 mg/dl	>3 mg/dl
Serum albumin	>3.5 g/dl	2.8-3.5 g/dl	<2.8 g/dl
INR	<1.7	1.71-2.20	>2.2
Ascites	No	Controlled	Poorly controlled
Encephalopathy	No	Controlled	Poorly controlled

Estimation of serum MEGX

Sampling & procedure: 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 an obturator. 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 [11].

Intravenous lidocaine was injected in a sub-therapeutic dose (1 mg/kg) over 1 min. Serum samples were obtained immediately before lidocaine injection (S_0) to assure absence of MEGX in serum and 15 (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 [11]. The amount of MEGX produced as a measure for detoxification and excretion functions of the liver was calculated as serum MEGX level at S_{30} minus S_{15}.

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 Wilxocon 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 30 cirrhotic patients; 22 males and 8 females with mean age of 44.2±5.4; range: 34-56 years and 10 controls; 7 males and 3 females with mean age of 43.7±5.9; range: 35-54 years. Patients' categorization according to CP classification defined 19 CP class A and 11 CP class B, (Table 2). All patients underwent laparoscopic surgical procedures; 13 patients had cholecystectomy, 6 patients underwent bilateral inguinal hernial repair, 7 patients had midline hernial repair, 3 patients had appendicectomy and one patient had bilateral varicocelectomy.

Mean operative time, irrespective of surgical procedure, was 60.8±15.1; range: 35-85 min and the mean duration of anesthesia was 76±19; range: 43.8-106 minutes. There was a non-significant (p>0.05) difference between patients categorized according to CP grades. Mean sevoflurane consumption was 310±30.9 MAC/hr with a non-significant (p >0.05) difference between patients categorized according to CP class.

All patients developed significantly higher HR and blood pressure measures at time of abdominal insufflations compared to baseline and returned to near baseline levels after exsufflation. There was non-significant (p>0.05) difference between patients categorized according to CP class as regard HR and blood pressure measures recorded throughout the operative time, (Table 3).

No patient had serum MEGX of >90 ng/ml in either sample. Twenty-nine patients had serum MEGX ranging between 50 and 90 ng/ml; 14 in S_{15} and 15 in S_{30}. Thirty-one patients had serum MEGX ranging between 50 and 90 ng/ml; 16 in S_{15} and 15 in S_{30}. In patients of preoperative CP class A and B, mean serum MEGX level estimated at S_{15} was non-significantly lower compared to that estimated at S_{30} with a mean increase of 5.3±2.5; range: 1.5-10 ng/ml in class A and 3.3±1.3; range: 1.4-5.2 ng/ml in class B. Moreover, patients of CP class B had significantly lower serum levels of MEGX at both 15 and 30 minutes compared to those who had preoperative CP class A, (Fig. 1).

Eight patients showed postoperative deterioration of CP clinical grading; 5 patients were CP class A deteriorated to class B, such deterioration was in form of increased serum aminotransferases apart from one patient who had postoperative hematemsis and progressed to hepatic coma. Three CP class B patients deteriorated postoperatively to class C, all showed flared up liver aminotransferases and increased serum total bilirubin levels and one patient developed progressive ascites that resisted control with concomitant melena and progressed to hepatic coma. Unfortunately, both patients who developed coma could not be compensated and died on the 5th and 7th postoperative day. One of these two patients had bilateral inguinal hernial repair and the second had midline hernia repair.

Despite the non-significant difference of serum MEGX estimated at 15 and 30 minutes after intravenous injection of lidocaine, patients ,who showed deterioration of CP class, showed the least difference between both samples with a negative significant correlation (r=-0.463, p =0.01) between S_{30}-S_{15} levels and possibility of deterioration. Moreover, both patients, who developed mortal deterioration, showed a difference of 1.5 and 1.4 ng/ml.

Table (2): Preoperative patients' data

		Control group (n=10)	Study group (n=30)		
			Child A (n=19)	Child B (n=11)	Total (n=30)
Age (years)		43.7±5.9 (35-54)	44.5±5.7 (35-56)	43.7±5 (34-51)	44.2±5.4 (34-56)
Gender; M:F		7:3	14:5	8:3	22:8
Child-Pugh data	Serum total bilirubin	0.94±0.17 (0.54-1.12)	1.7±0.19 (1.34-1.98)	2.3±0.16 (2.12-2.65)	1.94±0.33 (1.34-2.65)
	Serum albumin	5.09±0.42 (4.3-5.6)	3.18±0.27 (2.87-3.87)	3.82±0.11 (3.67-3.98)	3.42±0.38 (2.87-3.98)
	INR	1.12±0.09 (1.03-1.31)	1.49±0.13 (1.26-1.31)	1.91±0.19 (1.56-1.78)	1.65±0.26 (1.26-1.78)
	Ascites	0	0	Controlled	
	Encephalopathy	0	0	Controlled	

Data are presented as mean±SD & ratios; ranges are in parenthesis

Table (3): Hemodynamic changes occurred in studied patients throughout the duration of the procedure

	Timing Group	Baseline	Post insufflation	Post exsufflation
HR (beats/min)	Child A (n=19)	79.3±3.8	83.6±4.6*	80.7±2.8†
	Child B (n=11)	78.1±4.5	84.8±2.9*	81.3±2.1†
SBP (mmHg)	Child A (n=19)	117.2±4.7	126.1±5.1*	121.2±5.7†
	Child B (n=11)	115.9±6.5	125.7±7.1*	120±7.5†
DBP (mmHg)	Child A (n=19)	73.2±3	80.5±3.4*	76.5±3†
	Child B (n=11)	72.7±2.8	80.1±3.4*	76.2±3.2†

Data are presented as mean±SD

*: significant versus baseline measures †: significant Post insufflation

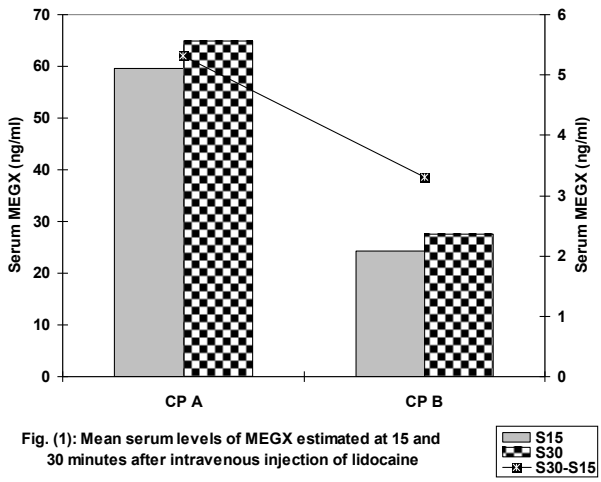

Fig. (1): Mean serum levels of MEGX estimated at 15 and 30 minutes after intravenous injection of lidocaine

4. Discussion

Abdominal surgery is generally considered to put patients with impaired liver function at high risk because it causes changes in hepatic blood flow and increases intraoperative bleeding because of high portal venous pressures, so the predictability of postoperative outcome of cirrhotic patients exposed to anesthetic and surgical risk during abdominal surgeries is still a mater of debate especially for patients with controlled manifestations of cirrhosis who were included in CP classes A and B; however, in those of class C, the risk is definite [12].

Elevated serum aminotransferases and total bilirubin with low serum albumin; the laboratory items for calculation of CP class, are always persistently elevated in these patients and could not represent all liver functions, so the reliance on these parameters or the clinical staging for prediction of postoperative morbidity and/or mortality is suspicious and multiple studies for evaluation of mere clinical grading scores reported discrepant results [13, 14].

Such discrepancy pushed multiple studies to try other parameters for evaluation of liver function and prediction of outcome of cirrhotic patients; ***Wanninger et al.*** [15] found portal and hepatic levels of galectin-3 to be negatively associated with liver function in patients with alcoholic liver cirrhosis and this may in part be related to impaired hepatic removal and/or increased synthesis in cirrhotic liver. ***La Mura et al.*** [16] found that in patients with cirrhosis and portal hypertension Von Willebrand factor levels correlate with liver function and independently predict clinical outcome. ***Wiest et al.*** [17] reported that impaired hepatic removal of IL-6 is explained by hepatic shunting and liver dysfunction in patients with liver cirrhosis partly explaining higher systemic levels

The current study tried to evaluate the determination of detoxification and excretory hepatic function as a guide for prediction of outcome using lidocaine as a substrate and its metabolite MEGX as a measure. Serum MEGX was non-significantly higher at 30 minutes after intravenous injection of lidocaine versus estimated levels at 15 minutes, irrespective of clinical class, but no patient approached the level of ≥90 ng/ml. A finding indicating deterioration of excretory and biodegradation function of liver after exposure to surgical and anesthetic risks. However, such impairment was more pronounced in patients of CP class B who showed significantly lower serum levels of MEGX at both 15 and 30 minutes compared to those had preoperative CP class A. Moreover, the extent of increase of MEGX serum levels, irrespective of preoperative CP class, showed a negative significant correlation with occurrence of postoperative deterioration of CP class and occurrence of postoperative morbidities that ended fatally in two patients.

These findings go in hand with that previously reported in literature concerning the predictability of estimation of serum MEGX as ***Botta et al.*** [18] who found MEGX serum levels were significantly different among patients who survived and those who died and serum creatinine, international normalized ratio and MEGX were independently associated with six month mortality while the same variables and the presence of ascites were associated with one year mortality. ***Sakka*** [19] found MEGX for lidocaine metabolism as an available dynamic test that may be recommended in critically ill patients for assessing liver function, liver blood flow and cell function.

Also, ***Bhise & Dias*** [20] reported that MEGX test is more discriminatory and recognizes early damage to the liver than conventional individual liver function tests.

Also, ***Hofmann et al.*** [7] 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 Child Turcotte Pugh class A cirrhosis and MELD scores of ≤8 in whom hepatic resection is needed. ***Lorf et al.*** [21] found preoperative MEGX-test, especially the 30 minutes 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.

In support of the correlation between serum MEGX and extent of liver injury, ***Ben Said et al.*** [22] 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 levels of transaminase levels and alteration of hepatocyte's structure with areas of necrosis.

In hand with the applicability of estimation of serum MEGX for prediction of cirrhotic patients outcome, ***Laviolle et al.*** [23] assessed liver function recovery after partial hepatectomy. MEGX serum level estimated 15 min after lidocaine injection on day 2 after surgery.And they found that estimation of MEGX correlate with liver function outcome.

Conclusion:

Estimation of serum MEGX is applicable and could be used as discriminative test for patients with varied degrees of liver cirrhosis and as predictor for prognosis after exposure to anesthetic and surgical risks.

Corresponding author
Wael ahmed Ibrahim
Anaesthesia NCI Cairo University
waelahmed60@yahoo.com

5.References

1. Telem DA, Schiano T, Goldstone R, Han DK, Buch KE, Chin EH, Nguyen SQ, Divino CM., 2010. Factors that predict outcome of abdominal operations in patients with advanced cirrhosis. Clin Gastroenterol Hepatol.; 8(5):451-7
2. Concha PM, Mertz KV., 2010. Perioperative risk among patients with cirrhosis. Rev Med Chil.; 138(9):1165-71.
3. Curvêlo LA, Brabosa W, Rhor R, Lanzoni V, Parise ER, Ferrari AP, Kondo M., 2009. Underlying mechanism of portal hypertensive gastropathy in cirrhosis: a hemodynamic and morphological approach. J Gastroenterol Hepatol.; 24(9):1541-6.
4. Bell CL, Jeyarajah DR., 2005. Management of the cirrhotic patient that needs surgery. Curr Treat Options Gastroenterol.; 8(6):473-80.
5. Bosch J, García-Pagán JC.,2000. Complications of cirrhosis. I. Portal hypertension. J Hepatol.; 32(1 Suppl):141-56.
6. del Olmo JA, Flor-Lorente B, Flor-Civera B, Rodriguez F, Serra MA, Escudero A, Lledó S, Rodrigo JM., 2003. Risk factors for nonhepatic surgery in patients with cirrhosis. World J Surg.; 27(6):647-52.
7. Hofmann WP, Rädle J, Moench C, Bechstein W, Zeuzem S., 2008. [Prediction of perioperative mortality in patients with advanced liver disease and abdominal surgery by the use of different scoring systems and tests]. Z Gastroenterol.; 46(11):1283-9.
8. Benedeto-Stojanov D, Nagorni A, Bjelaković G, Stojanov D, Mladenović B, Djenić N., 2009. The model for the end-stage liver disease and Child-Pugh score in predicting prognosis in patients with liver cirrhosis and esophageal variceal bleeding. Vojnosanit Pregl.; 66(9):724-8.
9. Moisés EC, Duarte Lde B, Cavalli Rde C, Marques MP, Lanchote VL, Duarte G, da Cunha SP., 2008.Pharmacokinetics of lidocaine and its metabolite in peridural anesthesia administered to pregnant women with gestational diabetes mellitus. Eur J Clin Pharmacol.; 64(12):1189-96.
10. Pugh RN, Murray-Lion IM, Dawson JL.,1973. Transection of the esophagus for bleeding esophageal varices. Br. J. Surg.; 60: 646.
11. Lorec A-M, Bruguerolle B, Attolini L, Roucoules X., 1994. Rapid simultaneous determination of lidocaine, bupivacaine and their two main metabolites using capillary gas-liquid chromatography with nitrogen-phosphorus detector. Ther Drug Monit, 16: 592.
12. Sabat A, Acosta Villegas F, Dalmau A, Koo M, Sansano Sánchez T, García Palenciano C., 2011. Anesthesia in the patient with impaired liver function. Rev Esp Anestesiol Reanim.; 58(9):574-81.
13. Shaikh S, Ghani H, Memon S, Baloch GH, Jaffery M, Shaikh K., 2010. MELD era: is this time to replace the original Child-Pugh score in patients with decompensated cirrhosis of liver. J Coll Physicians Surg Pak.; 20(7):432-5.
14. Neeff H, Mariaskin D, Spangenberg HC, Hopt UT, Makowiec F., 2011. Perioperative mortality

after non-hepatic general surgery in patients with liver cirrhosis: an analysis of 138 operations in the 2000s using Child and MELD scores. J Gastrointest Surg.; 15(1):1-11.
15. Wanninger J, Weigert J, Wiest R, Bauer S, Karrasch T, Farkas S, Scherer MN, Walter R, Weiss TS, Hellerbrand C, Neumeier M, Schäffler A, Buechler C., 2011. Systemic and hepatic vein galectin-3 are increased in patients with alcoholic liver cirrhosis and negatively correlate with liver function. Cytokine.; 55(3):435-40.
16. La Mura V, Reverter JC, Flores-Arroyo A, Raffa S, Reverter E, Seijo S, Abraldes JG, Bosch J, García-Pagán JC., 2011. Von Willebrand factor levels predict clinical outcome in patients with cirrhosis and portal hypertension. Gut.; 60(8):1133-8.
17. Wiest R, Weigert J, Wanninger J, Neumeier M, Bauer S, Schmidhofer S, Farkas S, Scherer MN, Schäffler A, Schölmerich J, Buechler C., 2011. Impaired hepatic removal of interleukin-6 in patients with liver cirrhosis. Cytokine. ;53(2):178-83.
18. Botta F, Giannini E, Romagnoli P, Fasoli A, Malfatti F, Chiarbonello B, Testa E, Risso D, Colla G, Testa R., 2003. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. Gut; 52(1):134-9.
19. Sakka SG., 2007. Assessing liver function. Curr Opin Crit Care; 13(2): 207-14.
20. Bhise SB, Dias RJ., 2007. Monoethylglycinexylidide (MEGX) as a liver function test in cirrhosis. Indian J Gastroenterol.; 26(4):167-9.
21. Lorf T, Schnitzbauer AA, Schaefers SK, Scherer MN, Schlitt HJ, Oellerich M, Becker H, Obed A., 2008. Prognostic value of the monoethylglycinexylidide (MEGX)-test prior to liver resection. Hepatogastroenterology.; 55(82-83):539-43.
22. Ben Said D, Ben Ali R, Ferchichi H, Salouage I, Ouanes L, Gaes E, Trabelsi S, Kooli E, Kourda N, Abdelmoula J, Lakhal M, Klouz A., 2011. Lidocaine test for easier and less time consuming assessment of liver function in several hepatic injury models. Hepatol Int.
23. Laviolle B, Basquin C, Aguillon D, Compagnon P, Morel I, Turmel V, Seguin P, Boudjema K, Bellissant E, Malleant Y.,2011. Effect of an anesthesia with propofol compared with desflurane on free radical production and liver function after partial hepatectomy. Fundam Clin Pharmacol.

6/6/2012