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Effect of Propofol Fentanyl Anesthesia on Hepatocellular Integrity During Induced Hypotension

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We undertook a study to evaluate the effects of propofol on hepatocellular integrity with or without nitroglycerin-induced hypotension using specific and sensitive markers of hepatic injury. In a randomized controlled study, thirty adult consented patients aged 22 to 55 years old scheduled for various urological procedures were allocated randomly to a nitroglycerin (NTG) or a control group (control) of fifteen patients each. Anesthesia was induced with fentanyl 2 $\mu g\ kg^{-1}$ and propofol 2 $mg\ kg^{-1}$. For maintenance, propofol infusion 6-10 $mg\ kg^{-1}\ h^{-1}$ and increments of fentanyl and atracurium were administered according to the monitored hemodynamic and neuromuscular responses, respectively. Induced hypotension was achieved in the NTG group using nitroglycerin infusion started at a rate of 0.5-1 $\mu g\ kg^{-1}\ min^{-1}$ and adjusted to maintain a mean arterial pressure (MAP) of 50-65 mm Hg. Hepatic glutathione S-transferases (α-GST and π-GST), hyaluronic acid (HA), aspartate (AST) and alanine (ALT) aminotransferases were measured before anaesthesia (T_0), 15 min (T_1), 30 min (T_2), 60 min (T_3) after reaching the target threshold of MAP and 24 h after the end of anesthesia (T_4). The control group showed no significant changes in plasma α-GST and hyaluronic acid concentrations while the NTG group showed significantly higher levels in hyaluronic acid from T_0 to T_1 ($p = 0.016$), T_2 ($p = 0.007$) and T_3 ($p = 0.003$). Also, α-GST was increased significantly in the NTG group from T_0 to T_2 ($p = 0.037$) and T_3 ($p = 0.049$). Both enzymes returned back to normal range 24 h after the procedures (T_4). π-GST, AST and ALT showed no significant changes throughout the study period in both groups. Propofol fentanyl anesthesia had no effect on plasma concentrations of GST and hyaluronate either during or after surgery. The addition of hypotension is associated with a transient reversible increase in these enzymes reflecting a minor degree of impaired hepatocellular integrity.

Key words: Propofol, induced hypotension, glutathione S-transferases (α-GST and π-GST), hyaluronic acid, hepatic integrity

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INTRODUCTION

With the acknowledgment that almost all anesthetic techniques reduce liver blood flow (Murray *et al*., 1992), it would seem wise that during procedures performed under hypotensive anesthesia, where further reduction of liver blood flow may be detrimental, the techniques and the agents used should be those having the least effect on liver blood flow and hepatocellular integrity. Renewed interest in the use of intravenous techniques to provide balanced anesthesia has been prompted partly by the concern of its potential to yield a compensated modulatory effects on the cardiovascular system, including preserved baroreflex activity (Win *et al*., 2007). Moreover, the use of propofol as part of a TIVA regimen seems to have no influence on hepatocellular function during and after surgery (Röhm *et al*., 2005). The measurement of the hepatic isoenzymes glutathione S-transferases (α-GST and π-GST) is a sensitive and specific method for the detection of acute and early drug-induced hepatocellular damage (Iwanaga *et al*., 2000). Serial studies demonstrated that the endothelial cell is a more susceptible target for the immune response than the hepatocyte. Since hyaluronic acid (HA) is utilized in assessing sinusoidal endothelial cell function and perfusion, thus measurement of serum hyaluronate concentration may even offer a better indicator in the early assessment of hepatocellular damage (Tran *et al*., 2000).

The purpose of this study was to assess the effects of propofol fentanyl anesthesia on hepatocellular integrity during nitroglycerin-induced hypotension using these specific and sensitive markers of hepatic injury.

MATERIALS AND METHODS

After obtaining personal informed consent and local ethics committee approval, 30 adult patients aged 22 to 55 years old of either sex (ASA class I or II) scheduled for various elective urological procedures (nephrolithotomy, nephrectomy) were studied in Theodor Bilharz Research Institute during the period from March 2005 till September 2006. Patients with previous liver disease, obesity, exposure to general anesthesia within the preceding 3 months, renal insufficiency (creatinine >1.5 mg dL^{-1}), unstable angina, severe uncontrolled hypertension or patients receiving medications likely to interfere with liver function were excluded from the study. When induced hypotension was believed to be beneficial, patients were randomly allocated to a control group (control, n = 15) and a study group (hypotension induced using nitroglycerin NTG, n = 15) using balanced total intravenous anesthesia (TIVA) with propofol (Propofol 1%, Fresinius Kabi Austria GmbH Graz, Austria) and fentanyl. Routine monitoring included five leads ECG, SpO_2, capnography, non invasive blood pressure, temperature, peripheral nerve stimulator as well as continuous invasive measurement of mean arterial blood pressure (MAP) (Infinity Kappa, Dräger, Lübeck, Germany). In both groups, IM midazolam 0.05 mg kg^{-1} was administered as premedication 30 min before induction of anesthesia, which was induced by fentanyl 2 μg kg^{-1}, propofol 2 mg kg^{-1} and tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1}. For maintenance, propofol infusion 6-10 mg kg^{-1} h^{-1} and increments of fentanyl 1 μg kg^{-1} and atracurium 0.15 mg kg^{-1} were administered according to the monitored hemodynamic and neuromuscular responses, respectively. Induced hypotension was achieved in the NTG group using nitroglycerin infusion started at a rate of 0.5-1 μg kg^{-1} min^{-1} and increased by the same increments at 2 min interval to maintain MAP of 50-65 mm Hg. A target threshold of MAP was defined as value of 80-90 mm Hg in the control group and 50-65 mm Hg in the NTG group. Hypotensive episodes were treated by increasing the rate of fluid administration and/or decreasing propofol infusion in both groups and reducing the rate of nitroglycerin infusion in the NTG group. By the end of surgery, propofol and nitroglycerin infusions were reduced so that MAP gradually returns nearly to its normal level. After anesthesia, patients were observed for 3 h in the post-anesthesia care unit and thereafter on the ward. Venous blood (5 mL each) was obtained from contra lateral antecubital vein of the infusion site before anesthesia (T_0), 15 min (T_1), 30 min (T_2), 60 min (T_3) after reaching the target threshold of MAP and 24 h after the end of anesthesia (T_4). Heparinized plasma was the preferred sample matrices. Blood samples were collected in lithium heparin tubes and centrifuged at 2500 g for ten minutes at 2-8°C within 6 h of collection. Plasma supernatant was decanted and re-centrifuged at 6000 g for 10 min at 2-8°C to ensure complete removal of platelets. Plasma was carefully collected by aspiration and stored at -20°C and samples were assayed for hepatic α-GST, π-GST and HA. α-GST was measured using the Biotrin High Sensitivity Alpha GST EIA Kit, Cat. No. BIO60HEPAS-96 wells. It is a quantitative enzyme immunoassay. π-GST was measured using the Biotrin Pi GST EIA-Hman GST-Pi Kit, Cat.No. Kat.Nr/cat Nb: BIO85-96 wells, which is also a quantitative enzyme immunoassay. HA measurement was performed using hyaluronic acid (HA) test kit (Corgenix Inc., Denver, Colorado, USA). Activity of AST and ALT was measured as routine hospital laboratory test analysis.

Statistical analysis was performed using SPSS software version 10. Data were expressed as

mean±standard deviation. Comparison between the two groups in the same time was done using Mann-Whitney U-test while comparison relative to the baseline in the same group was performed using Friedman's ANOVA with post-hoc Wilcoxon matched paired t-test. $p<0.05$ was considered statistically significant.

RESULTS

As regards the demographic data, the total dose of propofol and the perioperative values, including the duration of anesthesia and surgery, there was no statistical significant difference between the two groups. Blood loss as well the amount of crystalloid and colloid fluids given during the study period were significantly higher in the control as compared to the NTG group (Table 1). The MAP in the NTG group was significantly decreased by 15, 30 and 60 min compared with T_0 ($p<0.05$) as well as to the control group at the same timing whereas no difference was seen in other hemodynamic variables. These changes were reverted by the end of the procedure until 24 h afterwards (Table 2). Baseline values of α-GST, π-GST and HA concentrations were within normal range in all patients and comparable between both groups (Table 3). The control group showed no changes in plasma α-GST, π-GST and HA concentrations. α-GST increased significantly in the NTG group from T_0 (2849.0±642.4 ng L^{-1}) to T_2 (3171.0±914.6 ng L^{-1}; $p = 0.037$) and T_3 (3673.0±1623.7 ng L^{-1}; $p= 0.049$). HA in the NTG group showed also significantly higher levels from T_0 (19.9±3.96 ng mL^{-1}) to T_1 (21.6±4.77 ng mL^{-1}; $p = 0.016$), T_2 (24.7±4.97 ng mL^{-1}; $p = 0.007$) and T_3 (27.8±4.83 ng mL^{-1}; $p = 0.003$). Both enzymes returned back to normal range 24 h after the procedure (T_4). π-GST, AST and ALT showed no significant changes throughout the study period in both groups. No clinical signs or symptoms of hepatic disorders, gastroenterologic problems or systemic inflammatory disease were observed in any patient.

Table 1: Patient demographics, perioperative data and fluid therapy

Variables	Control	NTG
Age (year)	32.00±10.1	32.00±7.0
Sex (M/F)	10/5	9/6
Weight (kg)	65.80±10.7	71.20±11.6
ASA status (I/II)	12/3	13/2
Duration of anesthesia (min)	136.56±13.61	140.33±17.48
Duration of surgery (min)	120.51±16.19	115.12±14.42
Duration of hypotension (min)	------	84.30±11.4
Propofol (mg)	1022.69±256.3	1127.40±281.5
Blood loss (mL)	689.50±96.04*	361.00±66.07
Crystalloids (mL)	3180.00±493.96*	2225.00±547.34
Colloids (mL)	575.00±116.06	----

Data are expressed as mean±SD unless otherwise noted, Control = Control group (n = 15), NTG = Induced hypotension group (n = 15), *$p<0.05$, Intergroup comparison

Table 2: Mean Arterial Pressure (MAP) and Heart Rate (HR)

	MAP (mm Hg)		HR (bpm)	
Timing	Control	NTG	Control	NTG
T_0	89.2±7.29	91.0±8.09	84.3±9.14	83.1±8.28
T_1	85.8±6.96	63.3±3.27a*	85.1±8.75	82.7±7.41
T_2	89.1±5.82	62.9±3.33a*	83.6±7.64	80.9±6.73
T_3	91.0±5.77	59.7±4.75a*	82.9±7.53	81.8±6.35
End of anesthesia	90.7±5.90	89.5±5.60	85.0±6.70	82.9±7.50
T_4	91.6±6.40	92.5±6.49	83.4±8.18	84.3±7.83

Data are expressed as mean±SD, Control = Control group (n = 15), NTG = Induced hypotension group (n = 15), MAP = Mean arterial Pressure, HR = Heart rate, T_0 = Before anesthesia, T_1 = 15 min, T_2 = 30 min, T_3 = 60 min after reaching the target threshold of mean arterial pressure, T_4 = 24 h after the end of anesthesia, *$p<0.01$ versus the baseline value (T_0), a$p<0.01$ versus the control group at the same time

Table 3: Plasma α-GST, π-GST, HA, AST and ALT concentrations in the study groups

Enzyme	Groups	T_0	T_1	T_2	T_3	T_4
α-GST (ng L^{-1})	Control	3102.0±534.9	3124.0±435.7	3150.0±409.9	3309.0±448.1	3047.0±567.7
	NTG	2849.0±642.4	3040.0±861.9	3171.0±914.6*	3673.0±1623.7*	2909.0±817.9
π-GST (μg L^{-1})	Control	187.4±73.17	187.0±74.37	188.5±69.11	187.2±66.43	185.6±70.86
	NTG	207.2±64.59	210.4±62.05	212.2±63.88	213.4±63.0	208.9±64.82
HA (ng mL^{-1})	Control	21.6±4.22	21.9±4.91	22.3±5.89	22.5±5.62	21.0±3.620
	NTG	19.9±3.96	21.6±4.77*	24.7±4.97**	27.8±4.83**	19.9±3.980
AST (U L^{-1})	Control	22.5±4.81	22.1±4.23	22.3±5.44	22.4±5.39	21.3±4.740
	NTG	23.7±5.12	23.2±4.59	23.3±4.64	24.1±6.33	21.9±4.100
ALT (U L^{-1})	Control	24.4±4.01	23.7±5.74	25.6±5.64	25.1±4.48	22.5±5.760
	NTG	22.6±4.22	22.7±5.42	24.8±5.87	25.3±5.93	22.3±4.690

Data are expressed as mean±SD, α-GST = α-glutathione S-transferase, π-GST = π-glutathione S-transferase, HA = Hyaluronic acid, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, T_0 = Before anesthesia, T_1 = 15 min, T_2 = 30 min, T_3 = 60 min after reaching the target threshold of mean arterial pressure, T_4 = 24 h after the end of anesthesia, Control = Control group (n = 15), NTG = Induced hypotension group (n = 15), *$p<0.05$; **$p<0.01$ versus the baseline value (T_0)

DISCUSSION

Results from the present study suggest that propofol per se is not inclined to cause any distortion in the hepatocellular integrity whereas hepatocellular insult occurred only with superadded hypotension. Standard biochemical tests of liver function have limited use in the detection of minor degrees of anaesthetic-related liver dysfunction. In contrast, measurement of GST concentration in plasma provides a highly specific test of hepatocellular damage and their results correlate better with histological changes than do the aminotransferases (Sherman *et al*., 1983). Periportal hepatocytes contain the largest concentration of aminotransferases, but centrilobular hepatocytes, which are relatively deficient in ALT and AST, are more susceptible to damage from hypoxia (Redick *et al*., 1982). GST are readily and rapidly released into the circulation after hepatic injury; their short half-life ($T_{½}$< 90 min) allow earlier detection of hepatic damage than AST ($T_{½}$ 17 h) and ALT ($T_{½}$47 h) (Murray *et al*., 1994). Present results in the control group where hypotension was not elicited show no significant changes in α-GST throughout the study period as previously reported by Röhm *et al*. (2005) while using propofol-remifentanil anesthesia. Similar results have also been reported during and after 10 h of anesthesia with propofol (Murray *et al*., 1994). *In vitro* studies also showed that propofol did not exhibit significant inhibition of GST activity at concentrations less than 1.0 mmol L^{-1} (Chen *et al*., 2000). There are several possible explanations. GST activity is relatively low among phase-II enzymes in human liver making significant inhibition more difficult to detect (Chen *et al*., 2000). It may bind to a number of anions, such as bile salts, which might inhibit enzymic activity (Singh *et al*., 1980). Being a phenolic substitute, propofol might participate in the conjugation reactions as a hydrogen provider (functional anion) and bind with GST to reduce its conjugation ability (Deegan, 1992). Propofol has also been shown to decrease the grade of histopathologic injury to rat liver by decreasing apoptosis after gut ischemia/reperfusion through scavenging of reactive oxygen species and peroxynitrite as well as inhibiting lipid peroxidation (Kaplan *et al*., 2007). In contrast to present results, Tiainen *et al*. (1995), using a propofol infusion rate of 19 mg kg^{-1} h^{-1} without narcotic or muscle relaxant supplementation, reported a significant increase in α-GST from 3.1 to 10 μg L^{-1}. This increase is probably attributed to the use of such high infusion rate of propofol as a sole anesthetic. Additionally, Anand *et al*. (2001) reported a case of hepatocellular injury in a 17-year-old girl after propofol administration for 1 h 20 min. Liver biochemistries were performed 6 months before her admission with no clear preoperative data. Her previous general anesthetics had been associated with severe postoperative nausea and vomiting as well as a history of multiple drug allergies. As for π-GST in the control group, there was also no significant change. Being located in the cytoplasm of intrahepatic bile duct cells (Mattew *et al*., 1992), this might suggest that propofol does not have any effects on bile duct cell integrity. The serum hyaluronate concentration is influenced by the hepatic blood flow as a result of the delivery of hyaluronic acid to the liver (Arvidsson *et al*., 1989). Since no hemodynamic changes were noted in the control group, this might explain such lack of changes in plasma hyaluronate. Where literature on impact of different anesthetic agents on hepatic integrity is rather abundant, yet literature on their impact during hypotensive technique is rather scarce, especially when using GSTs as biomarkers. In accordance with our results, Suttner *et al*. (1999) reported a similar significant rise of α-GST during hypotensive anesthesia with sodium nitroprusside 90 min after anesthesia induction and returning back to normal 24 h after surgery. They reported a sustained significant rise 2 h postoperatively which might be related to the use of isoflurane. Moreover, their duration of hypotension appears to be a key factor in such changes since its rapid correction during spinal anesthesia (Ray *et al*., 2002) caused no disturbance of hepatocellular function as assessed by plasma GST. Autoregulation persists in vital organs such as the brain and the myocardium at MAP of 50 mm Hg, while in the gastrointestinal tract (GIT) and the liver; it exists only to a minor extent. Thus, systemic hypotension may lead to a decreased splanchnic perfusion and, subsequently, to a decreased oxygen delivery to the superficial mucosal lining of the GIT and the liver (Suttner *et al*., 1999). Maintaining a MAP at 80 mm Hg during prolonged anesthesia with propofol had no effects on the concentration of GST either during or after surgery (Murray *et al*., 1994). The significant increasing hyaluronan level in the NTG group indicates an undesirable reduction in effective sinusoidal perfusion as previously stated by Gibson *et al*. (1993). A static or decreasing level would permit a more extensive clinical evaluation to proceed with greater confidence as shown in the control group. No significant changes in aminotransferases were recorded either in the control group or the NTG group which goes in accordance with Robinson and Patterson (1985) as well as Fukusaki *et al*. (1997), respectively. Furthermore, when propofol was infused at a rate of 2.1 mg kg^{-1} h^{-1} with fentanyl for postoperative infant sedation in ICU for 48 h, it did not cause any hemodynamic disturbances and the hepatic

enzymes, AST, ALT and GGT did not increase significantly (Martin *et al*., 1997). Elevated serum levels of aminotransferase activity might be suggestive of hepatocellular damage. However, measurement of these enzymes lacks specificity, since a variety of organs other than the liver contain aminotransferases, which limit the usefulness of these enzymes as indicators of mild ischemic liver damage (Suttner *et al*., 1999).

CONCLUSION

We conclude that propofol fentanyl anesthesia had no effect on plasma concentrations of α-GST and HA either during or after surgery. The addition of hypotension is associated with transient reversible increase in these enzymes reflecting a minor degree of impaired hepatocellular integrity. Further studies would be recommended for assessing the margin of safety of propofol fentanyl anesthesia in patients with various degree of pre-existing hepatic dysfunction by serial measurements of α-GST and hyaluronic acid.

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