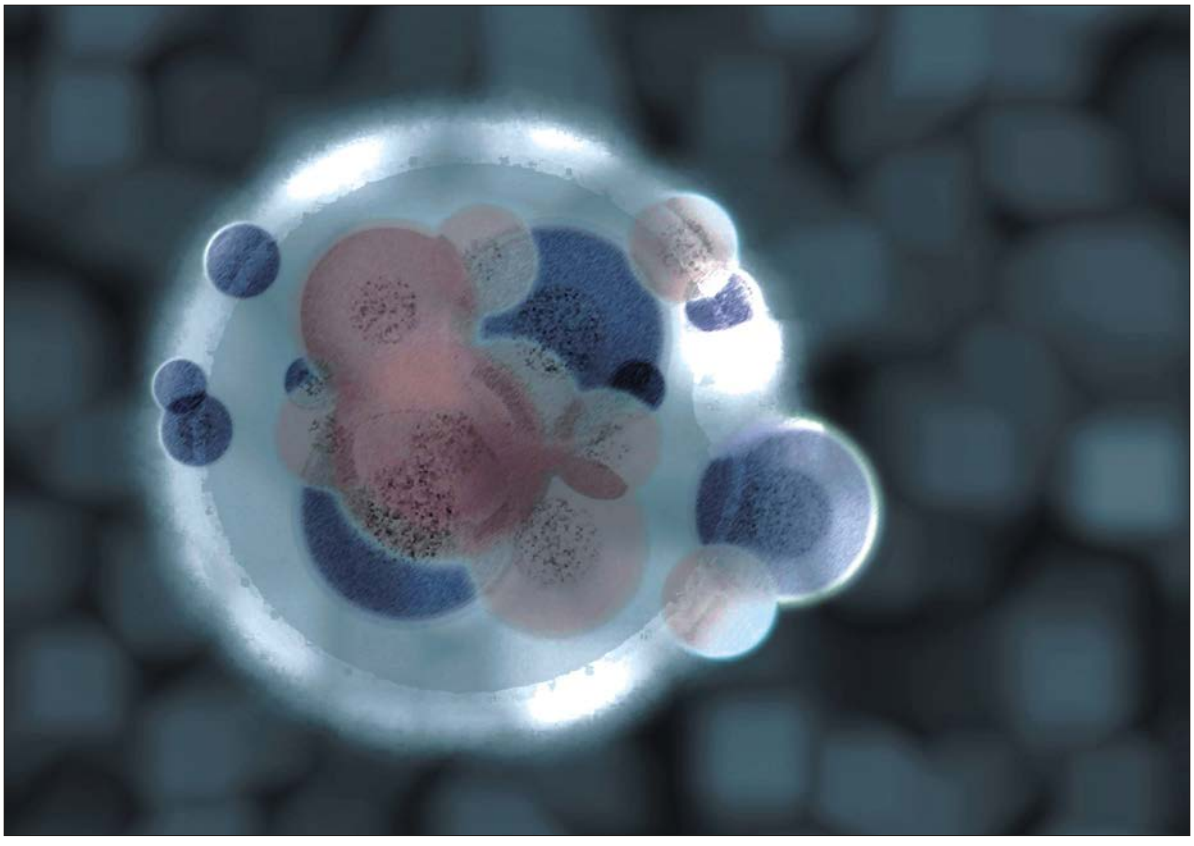

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Effect of Regional Epidural Ropivacaine Anesthesia on α-Glutathione-S-Transferase: Comparison with Low Flow Sevoflurane and Total Intravenous Propofol Anesthesia

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Abstract: This study presents the liver affection following low flow Sevoflurane anesthesia, total intravenous propofol anesthesia and regional epidural ropivacaine anesthesia in patients undergoing hysterectomy by using glutathione-S-transferase (α-GST) as a sensitive indicator of hepatocellular integrity as compared to the conventional liver enzymes. The study conducted on 45 healthy patients ASA I or II, scheduled for abdominal hysterectomy were randomly allocated into three equal groups. Group I received low flow Sevoflurane anesthesia, Group II received total intravenous propofol anesthesia and group III received regional epidural ropivacaine anesthesia. Three blood samples were drawn from each patient (preoperative, 2 and 24 h postoperative) and the measurements of blood glucose level, renal function tests, conventional liver enzymes and serum α-GST were done for all subjects. The results showed that, the conventional liver enzymes did not show any significant changes between the three studied groups, while the α-GST showed statistical significant difference between the three studied groups in the 2 h postoperative. A GST concentration was significantly increased in group I in the 2 h postoperative samples as compared to preoperative values and two other groups. While, in group II and group III there were no significant increase as compared to the preoperative values, although in group III the concentration of α-GST decreased but not significantly in the 2 h postoperative sample mostly due to hydration of the patients by the preloading fluid. The finding from this study suggest that, the epidural anesthesia has the least effect on liver functions especially when it was assessed by α-GST which is more specific and sensitive index for hepatic injury than the conventional liver enzymes. Epidural anesthesia should be considered as the anesthetic technique of choice for abdominal hysterectomy. Propofol also led to minimal effect on α-GST and a better quality of recovery than sevoflurane anesthesia, which caused mild elevation in GST and this may limit its use in patients with hepatic dysfunction.

Key words: Anesthetic techniques, sevoflurane, propofol, epidural, ropivacaine, hepatotoxicity, enzymes, α-GST

INTRODUCTION

The cytosolic liver enzyme α glutathione-S-transferase (α-GST) has been introduced as a specific and sensitive test for hepatocellular integrity and could express very minute trauma to liver cells as it correlates better with hepatic histology[1].

Conventional methods for assessing liver affection including the most commonly used transaminases namely alanine and aspartate transaminases (ALT and AST, respectively) had proved to be of poor organ specificity and lesser sensitivity. Their activity is increased by a wide variety of disorders not related to liver affection and thereby, so they should not be used solely for assessment of any drug induced hepatotoxicity. Unlike the aminotransaminases, which are predominantly found in the periportal hepatocyte, α-GST is found in high concentration (5% of soluble protein) in hepatocyte throughout the periportal and centrilobular regions of the liver[2]. Alpha GST is rapidly released from hepatocyte into blood in response to injury and its short plasma half-life (< 90 min) allows early detection of hepatic injury and the blood levels rapidly decline when the injury is resolved, these factors make α-GST the most sensitive hepatotoxicity biomarker. Subclinical hepatic injury after anesthesia continues to provoke interest, particularly with newer, most sensitive methods of assessment such as measurement of α-GST[3].

Impairment of hepatocellular integrity occurs after the administration of inhalational anesthetics, this may be either due to the direct hepatotoxic effect of the agent that has been used or due to the cardiovascular and

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hemodynamic effects of the anesthetic technique. Halothane, the most extensively metabolized agent, is associated with mild liver dysfunction in up to 30% of individuals exposed[4]. The new inhaled anesthetics (Desflurane and Sevoflurane) differ greatly in their resistance to *in vivo* metabolism. Desflurane is almost inert to biodegradation, with a calculated breakdown of 0.02%. However, small but significant levels of trifluoroacetic acid (TFA) were found after exposure to desflurane. The metabolism of sevoflurane is approximately 100 times greater (3–5%), but happens by different mechanisms and will therefore not form TFA. Hexafluoroisopropanol (HFIP) and inorganic fluoride are the main products of sevoflurane metabolism. The HFIP produced is transformed to HFIP-glucuronide, which is rapidly excreted by the kidneys[5,6]. Hence, the mild hepatic dysfunction occurring after sevoflurane anesthesia is not due to metabolic degradation but due to the decreased hepatic blood flow that might occur during anesthesia.

Clinical investigations of the effects of anesthetics on hepatocellular integrity indicate that liver function tests show transient increase in the activity of most enzymes after anesthesia with halothane and not sevoflurane or propofol. Eger and colleagues reported that sevoflurane, but not desflurane, caused small post-anesthetic increases in serum alanine aminotransferase (ALT), denoting mild and transient hepatic injury, suggesting that it is caused by compound A[7].

The present study was designed to evaluate the effect of anesthesia on hepatic cell function in patients undergoing hysterectomy under general anesthesia using sevoflurane versus total intravenous anesthesia using propofol or regional epidural anesthesia using ropivacaine and sufentamil. Alpha glutathione-S-transferase and other conventional liver enzyme activities were used to assess hepatic integrity. The main aim was to find the anesthetic technique of choice with the least effect on hepatic integrity.

MATERIALS AND METHODS

After taking the approval of the anesthesia department ethics and research committee, all patients included in this study gave a written informed consent. 45 healthy patients ASA I or II were studied who scheduled for abdominal hysterectomy in the Gynecology Department, Kasr El-Aini Hospital, Cairo University and they were allocated to one of the three groups using random number sequence:

Group I (15 patients): received general anesthesia using sevoflurane inhalational anesthetic.

Group II (15 patients): received total intravenous anesthesia using propofol.

Group III (15 patients): received epidural anesthesia with ropivacaine 0.75% and sufentamil 20 μg to achieve proper anesthesia to level T 4-6.

The exclusion criteria included obesity, previous history of liver disease, diabetes mellitus, recent exposure to anesthesia in the preceding three months and any contraindication for regional epidural anesthesia as bleeding disorders or previous spine surgery or infection at the site of lumbar epidural administration. All studied patients were subjected to full clinical assessment, general examination was done primarily to detect manifestation of liver cell dysfunction and associated illness. Liver and renal function tests and coagulation profile including bleeding, time, prothrombin time and concentration and partial thromboplastin time were performed for all patients. In addition glutathione-S-transferase concentration was also assessed.

All studied patients received 2.5 mg midazolam IV for sedation as a premedication and a prophylactic antibiotic of 1 gm Rocephin (Ceftriaxone) to exclude any hepatotoxic effect of different antibiotics. As regards group I, anesthesia was induced using sodium thiopental, at a dose of 3-5 mg kg^{-1}. Intubation was facilitated by suxamethonium 1 mg kg^{-1}. then anesthesia was maintained using atracurium 3-5 mg kg^{-1} as a muscle relaxant for controlled ventilation with a tidal volume of 8-10 ml kg^{-1} at a rate of 8-10 cycles per minute and sevoflurane at 2% average concentration at fresh gas flow rate of 2.5-3 L min^{-1} of oxygen and nitrous oxide at a ratio of 1:1 to maintain normocapnia as detected by end tidal carbon dioxide tension (34-38 mm Hg). The carbon dioxide absorbent was changed prior to administration of anesthesia in each case. Also the end tidal concentration of sevoflurane was measured using the gas analyzer and recorded. Arterial blood pressure was maintained to ±20% of the basal readings. After completion of the surgical procedure, the anesthetic was discontinued and fresh gas flow increased to 6 L min^{-1} of oxygen.

In Group II patients, anesthesia was induced by propofol 3-4 mg kg^{-1} and intubation was facilitative by suxamethonium at a dose of 1 mg kg^{-1} muscle relaxation was maintained by atracurium 3-5 mg kg^{-1} and controlled ventilation with a tidal volume of 8-10 ml kg^{-1} at a rate of 8-10 cycles per min with a total fresh gas flow of 8 L/min of Oxygen and nitrous oxide at a ratio of 1:1 to maintain normocapnia. Propofol infusion at a rate of 3 mg kg^{-1} h^{-1} was administered to maintain anesthesia and was discontinued at the end of the surgical procedure.

Group III received epidural anesthesia using a Tuohy needle 18 G at L 3-4 level and a 20 G catheter was introduced to maintain intra and post-operative analgesia with ropivacaine 0.75% and sufentanil 20 μg to achieve proper anesthesia to level T 4-6. These patients had an IV infusion of 1000 ml of lactated ringer solution prior to the epidural block. Hypotension (MAP <70% of baseline) was treated by IV ephedrine (12.5-25 mg).

Standard Intraoperative monitoring was carried out by a non invasive arterial blood pressure monitor every 5 min and a continuous electrocardiography, pulse oximetry and end tidal capnography (name of monitor).

Monitoring of the patients included non-invasive arterial pressure every 5 min and continuous electrocardiography, pulse oximetry and end-tidal CO_2 (Capnomac Ultima and Cardiscap, Datex, Helsinki, Finland) Hemodynamic state was assessed by calculating the mean of arterial blood pressure and heart rate during anesthesia.

Five ml of venous blood samples were drawn from each patient after an over night fast (preoperatively, 2 and 24 h postoperatively) then the samples were immediately centrifuged at 4°C and the serum was stored at -70°C until being thawed for analysis.

The samples were analyzed for: Fasting blood sugar level was estimated by God-PAP enzymatic calorimetric method using BioMerieux test kit, Cat. No. 5127.1 to be sure that all women were not diabetic[8].

Determination of serum aspartate transaminase (AST) and serum alamine tranaminase (ALT) levels by using the method recommended by the Committee on enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology[9], the test was performed using already commercially available kit from Boehringer-Mannhiem Company, Germany.

Determination of alkaline phosphatase activity by using the optimized standard enzymatic method according to the recommendation of the Committee on enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology[9], the test was performed using already available kit from BioMerieux Company, France.

Determination of α-GST concentration by use of enzyme immunoassay method using kit supplied from Biotrin International, Dublin, Ireland[2]. The test procedure is based on the sequential addition of sample, antibody-enzyme conjugate and substrate to micro-assay wells coated with anti α-GST-IgG. The resulted color intensity is proportional to the amount of α-GST present in serum.

Statistical analysis: Assuming that the concentrations of α-GST would be lesser in the epidural group than the sevoflurane group by 30%, the number of patients required in each group to observe such reduction was at least 10 with a = 0.05 and b = 0.08. Continuous parametric variables were presented as mean±standard deviation (SD). Comparison between groups was performed by one way and two way ANOVA testing using SPSS version 11.1 to detect statistical significant difference. P values <0.05 were considered significant.

RESULTS

Demographic data of the three studied groups found non-significant differences between the different studied groups as regards the age, weight, duration of surgery and the hospital discharge time (Table 1). Regarding the coagulation profile (bleeding time, prothrombin time and concentration and partial thromboplastin time) all patients included in this study were within the normal values and no significant difference between the studied groups.

Results of intra-operative hemodynamic changes (Table 2 and Fig. 1) revealed no statistical significant differences between the three studied groups as regards the preoperative data. However, during the intra-operative period the hemodynamic stability was better in the groups II and III compared to group I, the ANOVA testing performed within the same group showed no significant difference inspite of the statistical difference between the different groups. As regard to renal function tests (BUN and creatinine) and fasting blood sugar (Table 3) found all the patients were within the normal range and no significant difference between the studied groups.

Regarding the liver functions, in contrast to the increase in α-GST concentrations, no significant overall changes in routine liver function tests (ALT, AST and ALP) were found throughout the study. Alpha GST showed statistical significant difference between the three studied groups in the 2 h postoperative samples. In group I the α-GST concentration in the 2 h postoperative samples was significantly increase as compared to the preoperative values and the two other groups (Groups II and III). While, in group II there was a mild increase in α-GST concentration but not statistically significant, the increased levels return to the normal range in the 24 h postoperative samples in both groups (normal rang 0.75-1.29 ng ml^{-1}).

In group III the concentration of α-GST concentration decreased but not significantly in the 2 h postoperative samples mostly due to hydration of the patients by the preloading fluid, which return to the normal rang in the 24 h postoperative samples (Table 4 and Fig. 2).

Alpha GST showed high sensitivity and specificity about 93.3 and 93.3%, respectively at a cut off value 1.26 ng ml^{-1} in group 1 in the 2 h postoperative sample.

Table 1: Demographic data of the three studied groups

	Group I (n=15)	Group II (n=15)	Group III (n=15)
Age (years)	46.73±2.76	47.86±3.18	49.20±3.98
Weight (kg)	75.66±3.89	76.13±3.20	79.13±4.96
Duration of surgery (min.)	91.66±10.46	94.66±7.98	96.33±7.86
Duration of hosp. stay (days)	3.60±0.91	3.13±0.99	3.06±0.70

Group I: received general anesthesia using sevoflurane inhalational anesthetic.
Group II: received total intravenous anesthesia using propofol.
Group III: received epidural anesthesia with ropivacaine 0.75% and sufentanil 20 μg

Table 2: Hemodynamic parameters in the studied groups

		Group I (n =15)	Group II (n =15)	Group III (n =15)	Significance between groups
MAP	Preop.	103.26±4.90	104.29±4.20	103.30±6.30	NS
	15'	108.30±7.30	95.36±6.24	92.85±4.32	**
	30'	102.42±6.20	96.83±5.80	94.35±6.30	**
	60'	102.85±5.82	97.50±7.82	98.38±4.85	**
	Postop.	105.63±9.50	100.36±9.85	99.69±5.32	**
HR	Preop.	84.20±3.26	82.80±5.88	83.40±6.54	NS
	15'	82.60±4.80	72.60±6.35	78.62±5.80	**
	30'	80.65±7.80	75.39±9.37	79.38±6.49	*
	60'	81.89±8.32	73.78±8.65	78.64±8.32	*
	Postop	92.80±9.30	80.67±7.38	77.32±4.61	**

MAP: Mean arterial blood pressure, HR: heart rate NS: non-significant, * P<0.05 significant, ** P <0.01 highly significant

Table 3: Semm blood urea nitrogen, creatinine and fasting blood sugar in the different studied groups

		Group I (n =15)	Group II (n =15)	Group III (n =15)
BUN (mg/dL)	Preoperative	10.90±1.60	11.30±1.20	10.80±1.60
	Postoperative	11.01±1.50	12.10±1.10	12.50±1.40
Creatinine (mg/dL)	Preoperative	0.80±0.20	0.83±0.14	0.92±0.08
	Postoperative	0.82±0.17	0.82±0.11	0.87±0.10
FBS (mg/dL)	Preoperative	88.00±9.20	92.30±7.60	89.40±6.80

There were no significant changes P>0.05 in all the studied group, BUN: Blood urea nitrogen, FBS: Fasting blood sugar

Table 4: Serum ALT, AST, ALP and α-GST in the studied groups

		Group I (n=15)	Group II (n=15)	Group III (n=15)
ALT (IU/dL)	Preoperative	22.07±4.10	21.80±2.90	20.70±3.60
	2 h postoperative	27.61±4.50	23.20±2.50	21.60±3.40
	24 h postoperative	24.20±3.80	22.10±2.90	21.10±2.85
AST (IU/dL)	Preoperative	29.93±4.77	28.60±5.30	30.50±4.65
	2 h postoperative	31.60±5.45	33.30±4.80	30.90±5.13
	24 h postoperative	31.20±5.80	32.10±4.70	29.30±4.20
ALP (IU/dL)	Preoperative	140.75±5.10	134.86±8.35	150.10±2.30
	2 h postoperative	139.90±4.80	136.50±7.90	146.20±1.50
	24 h postoperative	142.30±5.20	140.20±6.50	150.90±5.20
Alpha GST(ng/ml)	Preoperative	0.99±0.14	0.95±0.18	0.98±0.11
	2 h postoperative	1.58±0.35*♦	1.11±0.20	0.92±0.09
	24 h postoperative	1.07±0.22	0.94±0.11	0.97±0.13

ALT: Alanine aminotranaminase, AST: Aspartate aminotransaminase, ALP: Alkaline phosphatase
* Significant increase P <0.05 within same group ♦ Significant difference between groups P>0.05

DISCUSSION

Subclinical hepatic injury after anesthesia continues to provoke interest, the results showed a short-lasting, statistically significant increase in α-GST concentrations after sevoflurane anesthesia and not after propofol or epidural ropivacaine, with preserved conventional liver function enzyme levels suggesting a mild disturbance of hepatocellular integrity. A reduction in hepatic blood flow in relation to metabolic demand might explain the temporary increase in a GST concentrations[10].

Results are agreed with study by Suttner *et al.*[6] who found that sevoflurane has a lower solubility in blood and tissues than all previously used volatile anesthetics. Impairment of hepatocellular integrity occurs after the administration of general anesthesia with all modern inhaled anesthetics. The cytosolic liver enzyme α-GST has been measured as a more sensitive marker of hepatocellular damage than conventional liver enzyme markers. Advantages of using α-GST as a marker of hepatocellular damage are the low molecular weight (51 kDa), a high cytosolic concentration (4–5% of total hepatocellular protein) and short circulatory half-life (<90 min). Consequently α-GST is rapidly released in quantity into circulation after hepatocellular damage and may be used as an indicator to track rapid changes in hepatocellular integrity.

Strunnin[11] stated that all anesthetic agents produce a decrease in portal venous blood flow proportional to the drop in systemic blood pressure. In

our study there was no significant reduction in mean arterial blood pressure (MAP) of the propofol group which might be the cause for preserved liver functions. Another study performed by Ray *et al.*[12] found that there was a statistically significant increase in α-GST concentration measured 1 h postoperatively and three out of their fifty studied patients showed secondary elevation in the 24 h postoperative samples. They concluded that the primary increase was due to the reduced hepatic blood flow and the secondary increase might have been due to the products of metabolism of sevoflurane. Also, Taivainen *et al.*[13] found that both halothane and sevoflurane may disturb hepatocellular integrity at 1-1.2 MAC of the volatile agent. They reported a small but significant increase in the postoperative concentration of α-GST. Another study concluded that Prolonged (8 h), high concentration (3%) sevoflurane anesthesia administered to volunteers in a fresh gas flow of 2 l/min does not result in clinically significant changes in biochemical markers of renal or hepatic dysfunction inspite of the statistically significant elevation in serum concentrations of α-GST detected in the first 2 days samples during the study[14] .

In a study performed by Suttner *et al.*[6] where they assessed the hepatic function in patients anesthetized with desflurane and sevoflurane, found that liver function as assessed by conventional liver enzymes were well preserved, whereas increased α-GST observed implied a reduction in splanchnic perfusion, leading to temporary impairment in liver oxygenation. These results were similar to those found in this study.

Obata *et al.*[15] concluded that low flow sevoflurane anesthesia have the same effect of isoflurane anesthesia on hepatic function as assessed by α-GST concentrations. The increase in the α-GST concentration was more significant than the results; this is due to the prolonged duration of anesthesia which was 338+92 min for the sevoflurane group compared 91.6+10 min in this study. Nesrine and Eman[16] compared the effect of combining epidural to general anesthesia with low flow sevoflurane, they found that there were no difference whether epidural was added or not and mild elevations in the concentrations of α-GST always occurred and that was not in concordance with our results because their patients received sevoflurane anesthesia in both groups and epidural anesthesia was added to one of the groups.

As regard the effect of propofol for total intravenous anesthesia on the hepatic integrity, there were no statistically significant changes in the conventional liver enzymes, although there was a mild increase in the concentration of α-GST in the 2 h postoperative sample, but this increment was not statistically significant. These results support a previous study by Murray and Trinick[17] that studied the effect of prolonged propofol anesthesia and assessed the hepatic function by α-GST and the hepatic clearance of indocyanine green. They found no significant changes throughout their study. Another study showed that prolonged anesthesia with propofol or isoflurane has no statistically significant on plasma concentrations of α-GST during and after extended surgery[18]. In a laboratory investigation performed by Chen *et al.*[19] in which they examined the effect of propofol on hepatic and extra hepatic conjugating systems, they found that it did not produce significant inhibition of human hepatic α-GST activity and they concluded that the effect of propofol on hepatic function should only be considered when using it with other anesthetics. Plasma glutathione-S-transferase concentration measurement is a sensitive and specific index of hepatocellular injury, α-GST concentration increases after anesthesia with most volatile anesthetic agents, but not after propofol. Such increases are thought to result from reduced liver blood flow[3]. These findings are in agreement with our results as we detected a mild increase in the concentration of α-GST concentration but not statistically significant, this might be due to the sensitivity of the kits that have been used for analysis.

The results, as regard the effect of epidural anesthesia using ropivacaine denoted that, there was no hepatic injury as defined by normal ALT, AST, ALP as well as α-GST levels postoperatively. These finding are in agreement with the only one study which assessed the effect of spinal anesthesia on liver function by α-GST estimation and they found that disturbance of hepatocellular function does not occur after spinal anesthesia when hypotension does not occur or is rapidly corrected with ephedrine[3]. The cause of reduction in the concentration of GST detected in our study might reflect changes in the hydration status due to the fluid preloading before starting the epidural technique. No previous studies were found comparing the effect of epidural anesthesia with general anesthesia on liver functions.

Regarding renal functions as assessed by creatinine and blood urea nitrogen, there were no statistically or clinically significant differences between the studied groups in the postoperative samples. These findings are supported by the study presented by Ebert and Shahbaz[20] who concluded that the clinical use of approximately 1 MAC sevoflurane in a FGF of only 1 l/min for lengthy procedures did not have clinically significant adverse effects on renal function. Another studies showed also that there were no effects produced by anesthesia on renal functions so long the hemodynamics

of the patients is preserved[21-23]. Several studies found that, the renal tubular and hepatic effects of low-flow sevoflurane and isoflurane were similar as assessed using both conventional measures of hepatic and renal function[24-26].

From this study it can be concluded that the use of epidural anesthesia has the least effect on liver functions especially when it was assessed by α-GST which is more specific and sensitive than the conventional liver enzymes and it should be considered as the anesthetic technique of choice for abdominal hysterectomy whenever it is not contraindicated. Epidural carries the benefit of better postoperative control on pain, early ambulation and lesser risk of deep venous thrombosis. Propofol also led to minimal effect on α-GST and a better quality of recovery than sevoflurane anesthesia, which caused mild elevation in α-GST and this may limit its use in patients with hepatic dysfunction. Further studies are recommended in which combination of sedation using propofol with epidural during hysterectomy should be assessed. Also, further studies are needed to investigate the effect of epidural on patients with hepatic dysfunction.

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