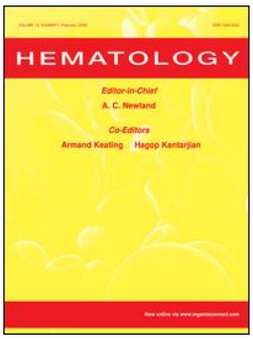

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Effect of general and epidural anesthesia on hemostasis and fibrinolysis in hepatic patients

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This study was designed to compare the effect of general anesthesia using isoflurane and epidural anesthesia using ropivacaine on hemostasis in hepatic patients. Sixty patients were randomly allocated into two groups to receive either general or epidural anesthesia which further subdivided into control and hepatic subgroups. Blood samples were collected preoperatively, immediate post-operatively and on third post-operative day to measure hemoglobin (Hb), platelet count (PLT),), prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time (TT). Specific hemostatic and fibrinolytic parameters were also included; von Willebrand factor (vWF), soluble platelet selectin (sP-selectin), prothrombin fragment (PF_{1+2}), tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1) and D-dimer. Hemoglobin showed a significant post-operative decrease in all subgroups. Post-operative changes of PLT, PT, PTT and TT were comparable between general and epidural anesthesia. General anesthesia showed a marked significant increase in specific parameters compared to epidural anesthesia. This study concluded that epidural ropivacaine anesthesia provided better hemostatic stability especially in hepatic patients.

Keywords: Epidural, general, anesthesia, hemostasis, hepatic

Introduction

Hemostasis following trauma or surgery is dependent on vascular contraction, formation of platelet plug (primary hemostasis) and blood coagulation (secondary hemostasis). Soluble platelet selectin (sP-selectin) released into the blood stream from platelet surface indicates platelet activation.[1] Plasma von Willebrand factor (vWF) is a marker of endothelial cell injury while prothrombin fragment 1+2 (PF_{1+2}) is a marker of coagulation activation.[2] There is a delicate balance between tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI) in the process of fibrinolysis to maintain normal intravascular fluidity.[1] Plasmin degrades fibrin and fibrinogen producing D-dimer and fibrin degradation products respectively. D-dimer is the final product of the simultaneous activation of blood coagulation and fibrinolysis.[3] Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are by far the most common screening tests for global coagulation abnormalities. These tests correspond respectively to extrinsic and intrinsic pathways of the Waterfall/Cascade coagulation.[4] While thrombin time (TT) is a sensitive indicator for deficiency of fibrinogen or inhibition of thrombin.[1]

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During surgery, there are major disturbances in coagulation and inflammatory systems because of hemorrhage/hemodilution, blood transfusion and surgical stress.[4] Acute inflammatory responses associated with vascular injury and wound healing often result in elevated cytokines, platelet count, fibrinogen, vWF-Factor VIII, and PAI-1 levels above the normal limit.[5] In severe hemodilution, anticoagulant proteins become progressively decreased.[6] During the post-operative period there is an imbalance between procoagulant and anticoagulant elements that may increase the risk for prothrombotic complications.[7]

Epidural and spinal anesthesia seem to reduce the frequency of deep vein thrombosis and pulmonary embolism and reduce intra- and post-operative blood loss due to hyperkinetic blood flow in the lower limbs, reduced tendency to coagulation and improved fibrinolytic function.[8] Ropivacaine is an amino amide local anesthetic that does not appear to produce clinically significant alterations in clotting or fibrinolysis.[9] General anesthesia, however, causes activation of coagulation and fibrinolysis followed by depression of fibrinolysis.[10] There are conflicting results regarding the use of isoflurane with nitrous oxide anesthesia, some have shown that platelet aggregation is significantly reduced,[11] but others have shown no effect either intra- or post-operatively.[12]

The liver plays a key role in hemostasis. It is the site of synthesis of all coagulation factors, except for vWF, fibrinolytic parameters and their inhibitors. Chronic liver disease is frequently associated with hemostatic derangements and these patients can experience severe bleeding or even thrombotic complications.[13] General anesthesia and surgery may lead to complications in patients with well-compensated or occult cirrhosis, and may result in considerable morbidity and mortality. General anesthesia can induce liver damage, through decreased liver blood flow, increased intracellular calcium concentration, or immune response directed against hepatic proteins altered by metabolites of anesthetics. Isoflurane seems to be better than other anesthetics for hepatic patients because of its low liver metabolism.[14] The pharmacokinetics of the majority of local anesthetics is affected by a poor liver function.[15]

Anesthestists are involved not only in the perioperative management of patients with coagulopathy or those on anticoagulant or antiplatelet drugs but also participate in reducing the incidence of arterial and venous thrombosis and hence decreasing the morbidity from cerebrovascular, coronary artery disease or pulmonary embolism. Moreover, it is possible that some anesthetic agents may protect against intravascular thrombosis during surgery.[16]

The aim of this study was to assess and compare the intra- and post-operative effect of general anesthesia using isoflurane and epidural anesthesia using ropivacaine on coagulation and fibrinolysis. The study was performed on patients with chronic liver disease and control subjects with normal liver in a trial to find out the best anesthetic agent and technique with the least effect on hemostatic mechanism in such patients.

Patients and methods

This study was conducted on patients admitted to Theodore Bilharz Research Institute after approval of the institutional ethical committee and obtaining an informed consent from every patient. The study involved 60 adult patients aged between 25 and 55 years of either sex, American Society of Anesthesiology (ASA) I–II scheduled for various lower abdominal operations for bladder stones, stones lodged in the lower end of the ureter, varicocelectomy and herniorrhaphies. Using computer generated random numbers, patients were assigned into one of two main groups (30 patients each): Patients received general anesthesia (Group G) using isoflurane and a second group in which patients received epidural anesthesia (Group E) using ropivacaine. Each group of general and epidural anesthesia was further subdivided equally into control subgroup who had normal liver (G-C, E-C subgroups respectively) and hepatic subgroup having chronic liver disease (G-H, E-H subgroups respectively). Hepatic cases were of Child class A or B and proved to have viral hepatitis and/or schistosomiasis. Patients with severe weight loss, obesity, pregnant or lactating women, malignant, feverish or septic cases were excluded from the study. Patients with history of hemostatic abnormalities, those on medications known to affect hemostasis, or who required blood or colloid transfusion were also excluded.

All patients were premedicated with intravenous (IV) administration of 0·05 mg/kg midazolam half an hour before induction of anesthesia. Routine monitoring included five leads ECG, SpO_2, end tidal CO_2, non-invasive blood pressure, temperature and peripheral nerve stimulator (Infinity Kappa, Dräger, Lübeck, Germany) had been attached to the patients. Baseline readings were recorded then every 5 minutes till the end of the procedure. Preload by IV infusion of acetated ringer 6–7 ml/kg was given then continued intraoperatively to maintain hemodynamic

stability. Mean arterial pressure 20% lower than baseline or <60 mmHg was treated with IV ephedrine 6 mg. Bradycardia defined as heart rate <40 beat per minute was treated by atropine 10 μg/kg. Normothermia was maintained during surgery.

General Anesthesia Group (group G): induction of anesthesia was initiated by fentanyl (1–2 μg/kg IV) and thiopentone (4–7 mg/kg IV) which were titrated to loss of consciousness. Maintenance of anesthesia was achieved using 1–1·5% isoflurane in a mixture of oxygen–air. Atracurium 0·5 mg/kg was given to facilitate endotracheal intubation and intraoperative muscle relaxation. The lungs were mechanically ventilated to maintain normocapnia. Incremental doses of IV fentanyl (1 μg/kg) and atracurium (0·1 mg/kg) were given as required intraoperatively. At the end of surgery, residual neuromuscular block was antagonized by neostigmine (40 μg/kg) and atropine (20 μg/kg).

Epidural Anesthesia Group (group E): local anesthesia was infiltrated at L2–3 level then lumbar epidural with loss of resistance technique was employed. A 20 gage catheter was introduced through an 18 gage epidural needle (B. Braun, Melsungen, Germany). A test dose of 3 ml lidocaine 20 mg/ml with adrenaline 5 μg/ml was used to exclude both subarachnoid and intravascular injection. A bolus dose 10–15 ml of ropivacaine 0·75% (Naropen, AstraZenca, Sweden) (75–112·5 mg) was injected incrementally. After two-segment regression had occurred, one-third of the initial activation dose was reinjected.

Post-operative analgesia in general group was provided by 50 mg meperdine given intravenously every 6 hours. In epidural group ropivacaine 0·2% was infused at a rate of 5 ml/h.

Post-operative evaluation: three days post-operatively all patients were assessed hemodynamically every 6 hours and were evaluated for detection of possible complications as ascites, hepatic encephalopathy, upper gastrointestinal bleeding, hepatorenal syndrome, liver failure and coagulopathy.

Hematological studies

Blood samples were collected three times; immediately before operation, immediately after operation and on the third post-operative day. Venous blood was collected under aseptic conditions by clean venepuncture, without frothing and with minimal venous stasis using vacuum tubes. Blood samples were collected in EDTA anticoagulated tubes to perform hemogram with platelet counting using automatic hematology analyzer Celltac – MEK 8118 (Nihon Kohden, Japan), and in sodium citrate anticoagulated tubes to perform the screening tests (PT, PTT and TT) and specific hemostatic and fibrinolytic tests (vWF, sP-selectin, PF_{1+2}, tPA, PAI-1 and D-dimer). The citrated blood was centrifuged for 20 minutes at 3000 rpm, and the supernatant plasma was separated. The screening coagulation tests were performed immediately after the separation and the remaining plasma was aliquoted and stored at $-70^{\circ}C$ until used to perform the specific hemostatic and fibrinolytic tests.

The screening coagulation tests were performed by the Fibrintimer (Behringwerke AG, Marburg, Germany). They included measuring of *prothrombin time* by using Thromborel S reagent (Behringwerke AG), *partial thromboplastin time* by using Pathromtin reagent (Behringwerke AG) and *thrombin time* by using Test Thrombin reagent (Behringwerke AG).

The specific hemostatic and fibrinolytic tests were measured including; *von Willebrand factor* by ELISA kit (vWF activity, REAADS Medical Products Inc., Westminster, CO, USA), *soluble platelet selectin* using ELISA kit (Quantikine sP-selectin, R&D Systems Inc., Minneapolis, MN, USA), *prothrombin fragment 1+2* by ELISA kit (Enzygnost PF_{1+2}, Behringwerke AG), *tissue plasminogen activator* and *plasminogen activator inhibitor-1* by the use of Zymutest, tPA antigen and Zymutest, PAI-1 antigen (Hyphen BioMed, Neuville sur Oise, France) ELISA kits respectively. *D-dimer* concentration was also measured by ELISA kit (Zymutest, D-dimer, Hyphen BioMed, France). All tests were performed following the manufacturers' instructions.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) or number. Comparison between the mean values of the two groups was done using Mann–Whitney U test, while comparison relative to the baseline in the same group were performed using Friedman's ANOVA with *post hoc* Wilcoxon matched pairs test. *P* value equal to or less than 0·05 was considered significant. Statistical analysis was performed with the aid of the SPSS computer program (version 12 windows).

Results

No significant difference was observed between the four studied subgroups concerning demographic data; age, weight, height, body mass index (BMI) and gender as well as the duration of surgery (Table 1). All cases with normal liver were classified as ASA class I, while hepatic patients were of ASA class II. Among hepatic cases in both types of

Table 1 Demographic data and duration of surgery

	G-C (n=15)	G-H (n=15)	E-C (n=15)	E-H (n=15)
Age (years)	37·5±14·2	44·1±4·6	34·9±10·9	42·5±7·9
Weight (kg)	81·3±7·2	80·0±8·9	76·5±6·1	76·7±9·4
Height (cm)	165·2±9·8	162·4±7·4	159·7±7·1	167·1±3·3
BMI (kg/m^2)	30·0±3·5	30·4±3·5	30·1±3·0	27·5±3·5
Gender (M : F)	9 : 6	8 : 7	7 : 8	9 : 6
Duration of Surgery (minutes)	136·0±15·5	126·0±12·4	126·0±12·4	151·2±25·0

Data are expressed as mean±SD or number.
G-C, control cases anesthetized generally; G-H, hepatic cases anesthetized generally; E-C, control cases anesthetized epidurally; E-H, hepatic cases anesthetized epidurally; BMI, body mass index.

anesthesia, no statistically significant difference of Child–Pugh classification (Child A/B) being (9/6) in patients anesthetized generally and (10/5) in patients anesthetized epidurally.

There was no significant difference between the four studied subgroups regarding total protein, blood urea and serum creatinine. As expected, hepatic patients had significantly higher aspartate (AST) and alanine (ALT) aminotransferases and significantly lower albumin when compared to control cases within the similar anesthetic subgroups (Table 2).

A significant decrease in mean hemoglobin concentration was recorded in the four subgroups post-operatively when compared with their corresponding preoperative values (Table 3). Pre- and post-operatively, hepatic patients showed a significant lower mean platelet count and a significant longer duration of the screening coagulation tests (PT, PTT and TT) when compared with their corresponding control cases within similar anesthetic subgroups (Table 3). Preoperative values of PT, PTT and TT were within accepted reference values in the control subgroups and slightly elevated in the hepatic subgroups.

The specific hemostatic and fibrinolytic tests (vWF, sP-selectin, PF_{1+2}, tPA, PAI-1 and D-dimer) revealed immediate post-operative marked significant elevation with general anesthesia, which was reverted after 3 days but not to the baseline. Meanwhile, modest elevation was observed with epidural anesthesia, which was reverted to near baseline level after 3 days. Hepatic cases showed significant higher values of specific hemostatic and fibrinolytic parameters when compared with the corresponding control cases in the similar anesthetic subgroups pre- and post-operatively. Both control and hepatic cases anesthetized epidurally showed post-operative statistical significant lower mean values of these parameters when compared with their corresponding control and hepatic patients anesthetized generally (Table 4).

No post-operative complications could be detected in normal or hepatic cases whether anesthetized generally or epidurally.

Discussion

This study showed significant post-operative decrease in hemoglobin level and non-significant increase in platelet count but both within clinically acceptable range. Post-operative changes of screening coagulation tests (PT, PTT and TT) were mostly comparable between general and epidural anesthesia. General anesthesia using isoflurane resulted in a significant increase in specific hemostatic and fibrinolytic parameters (vWF, sP-selectin, PF_{1+2}, tPA, PAI-1 and D-dimer) whether the liver condition was normal or compromised when compared to epidural anesthesia with ropivacaine. Meanwhile these variables were transient and reversible. Hepatic cases showed

Table 2 Preoperative laboratory data

	G-C (n=15)	G-H (n=15)	E-C (n=15)	E-H (n=15)
AST (U/l)	21·0±8·4	65·6±22·6$^{\#}$	19·1±4·4	40·5±22·2$^{\$}$
ALT (U/l)	18·0±3·5	42·1±5·8$^{\#}$	17·3±31·0	44·9±26·3$^{\$}$
Total Protein (g/dl)	7·6±0·3	7·2±0·8	7·3±0·6	7·0±0·6
Albumin (g/dl)	4·5±0·3	3·5±1·0$^{\#}$	4·4±0·2	3·9±0·5$^{\$}$
Urea (mg/dl)	26·7±5·2	32·7±6·8	34·5±9·9	32·8±8·6
Creatinine (mg/dl)	0·9±0·1	0·8±0·2	0·9±0·2	0·9±0·1

Data are expressed as mean±SD.
G-C, control cases anesthetized generally; G-H, hepatic cases anesthetized generally; E-C, control cases anesthetized epidurally; E-H, hepatic cases anesthetized epidurally.
AST, aspartate aminotransferase; ALT, alanine aminotransferase.
$^{\#}P<0·05$ relative to group G-C at the same timing; $^{\$}P<0·05$ relative to group E-C at the same timing.

Table 3 Mean pre- and post-operative (PO) hemoglobin, platelet count and screening coagulation tests

		G-C (n=15)	G-H (n=15)	E-C (n=15)	E-H (n=15)
Hb (g/dl)	Pre	12·8±1·2	11·7±1·0	13·5±0·9	11·7±1·0
	PO	11·7±1·3*	10·6±1·1*	12·4±1·3*	10·7±1·0*
	3rd PO	12·1±1·1*	10·9±1·1*	12·7±1·1*	10·9±1·1*
PLT count ($\times 10^9$/l)	Pre	303·7±69·4	137·7±45·1$^{\#}$	275·2±63·8	144·2±38·5$^{\$}$
	PO	312·5±62·3	152·3±59·8$^{\#}$	299·6±78·1	153·9±40·3$^{\$}$
	3rd PO	319·9±63·7	147·4±52·3$^{\#}$	293·8±74·4	158·6±54·0$^{\$}$
PT (seconds)	Pre	12·8±0·9	16·3±1·4$^{\#}$	13·0±0·5	15·8±1·1$^{\$}$
	PO	12·2±1·0	16·2±1·2$^{\#}$	13·0±0·5	15·5±1·2$^{\$}$
	3rd PO	13·4±1·2	16·7±1·5$^{\#}$	13·0±0·7	15·7±1·3$^{\$}$
PTT (seconds)	Pre	31·0±2·4	42·2±3·5$^{\#}$	32·0±2·8	43·0±2·5$^{\$}$
	PO	30·4±2·2	40·9±3·7$^{\#}$	31·1±2·9	42·6±2·9$^{\$}$
	3rd PO	31·1±2·3	44·2±4·1$^{\#}$	32·4±3·0	42·9±2·6$^{\$}$
TT (seconds)	Pre	16·9±1·4	27·0±2·6$^{\#}$	17·2±1·4	29·3±3·3$^{\$}$
	PO	16·8±1·4	26·6±2·9$^{\#}$	16·6±1·3	29·1±3·2$^{\$}$
	3rd PO	17·4±1·5	27·8±2·5$^{\#}$	16·9±1·3	29·6±3·6$^{\$}$

Data are expressed as mean±SD.
G-C, control cases anesthetized generally; G-H, hepatic cases anesthetized generally; E-C, control cases anesthetized epidurally; E-H, hepatic cases anesthetized epidurally.
*P<0·05 relative to preoperative reading in each group; $^{\#}P$<0·05 relative to group G-C at the same timing; $^{\$}P$<0·05 relative to group E-C at the same timing.
Hb, hemoglobin concentration; PLT, platelet count; PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time.

pre- and post-operatively significantly higher values of the specific hemostatic and fibrinolytic parameters when compared with the corresponding control cases in the similar anesthetic subgroups.

The significant post-operative decrease in hemoglobin level observed in all patients included in the study, is expected due to intraoperative hemodilution. Minimal blood loss occurred in all groups and was comparable. Similar results were obtained by Brueckner *et al.*,[17] who compared the effect of general and spinal anesthesia on hemoglobin and hemostatic markers.

Concerning the screening coagulation tests, there were comparable changes in patients receiving general and epidural anesthesia. This goes in accordance with Donadoni et al.,[18] who found no difference concerning PT and PTT in patients receiving general, epidural or combined general–epidural anesthesia. Contrary to Brueckner et al.,[17] who found that PT and TT showed a significant decrease 2 hours after skin incision in

Table 4 Mean pre- and post-operative (PO) specific hemostatic and fibrinolytic tests

		G-C (n=15)	G-H (n=15)	E-C (n=15)	E-H (n=15)
vWF (%)	Pre	58·5±6·0	94·9±10·6$^{\#}$	61·1±6·3	97·7±12·7$^{\$}$
	PO	90·7±11·0*	135·4±20·1$^{\#}$*	66·9±7·8$^{\#}$*	103·9±13·6$^{a\$}$*
	3rd PO	74·8±8·6*	114·0±12·2$^{\#}$*	64·7±7·1$^{\#}$*	102·8±12·5$^{a\$}$*
sP-selectin (ng/ml)	Pre	33·0±9·6	72·8±10·6$^{\#}$	34·5±5·9	74·3±12·5$^{\$}$
	PO	72·2±16·2*	140·4±29·1$^{\#}$*	39·3±5·8$^{\#}$*	78·9±11·9$^{a\$}$*
	3rd PO	54·5±13·5*	102·7±14·1$^{\#}$*	37·3±5·9$^{\#}$*	75·5±11·7$^{a\$}$
PF_{1+2} (nmol/l)	Pre	0·6±0·1	1·5±0·4$^{\#}$	0·5±0·1	1·9±0·2$^{a\$}$
	PO	2·1±0·4*	3·6±0·5$^{\#}$*	1·0±0·2$^{\#}$*	2·7±0·5$^{a\$}$*
	3rd PO	1·7±0·4*	2·8±0·4$^{\#}$*	0·8±0·2$^{\#}$*	2·3±0·3$^{a\$}$*
tPA (ng/ml)	Pre	5·3±1·0	11·8±1·1$^{\#}$	5·6±1·2	12·1±1·0$^{\$}$
	PO	12·1±1·9*	21·6±2·2$^{\#}$*	9·8±1·6$^{\#}$*	17·2±1·4$^{a\$}$*
	3rd PO	9·5±2·0*	18·2±2·0$^{\#}$*	7·7±1·3$^{\#}$*	14·9±1·4$^{a\$}$*
PAI-1 (ng/ml)	Pre	14·4±2·7	27·3±2·9$^{\#}$	14·1±2·5	28·5±3·6$^{\$}$
	PO	27·1±4·8*	42·8±3·1$^{\#}$*	20·9±3·3$^{\#}$*	37·3±4·0$^{a\$}$*
	3rd PO	24·5±4·6*	38·7±3·3$^{\#}$*	18·5±3·1$^{\#}$*	34·4±4·4$^{a\$}$*
D-dimer (ng/ml)	Pre	284·7±64·4	720·0±170·9$^{\#}$	276·7±47·8	766·7±169·7$^{\$}$
	PO	511·7±101·8*	1053·3±223·2$^{\#}$*	319·7±63·8$^{\#}$	830·3±176·4$^{a\$}$
	3rd PO	361·3±77·9*	913·5±154·6$^{\#}$*	283·0±50·1$^{\#}$	783·2±145·8$^{a\$}$

Data are expressed as mean±SD.
G-C, control cases anesthetized generally; G-H, hepatic cases anesthetized generally; E-C, control cases anesthetized epidurally; E-H, hepatic cases anesthetized epidurally.
*P<0·05 relative to preoperative reading in each group; $^{\#}P$<0·05 relative to group G-C at the same timing; $^{\$}P$<0·05 relative to group E-C at the same timing; ^{a}P<0·05 relative to group G-H at the same timing.
vWF, von Willebrand factor; sP-selectin, soluble platelet selectin; PF_{1+2}, prothrombin fragment $_{1+2}$; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1.

general and spinal groups. The prolonged duration of PT, PTT, and TT found in hepatic cases of this study may be due to impaired hepatic synthesis of coagulation factors in association with increased activity of sialil-transferase in immature hepatocytes, which leads to formation of fibrinogen with increased sialic acid content (dysfibrinogenemia).[19]

A significant lower mean platelet count was observed in the hepatic group in comparison to the control group within the similar type of anesthesia but all readings were within clinically accepted range. There was no significant post-operative change of platelet count within each subgroup whether patients anesthetized epidurally or generally. The same effect of isoflurane was recorded by Brueckner *et al.*[17]

In the present study, the post-operative significant increase in sP-selectin with general anesthesia points to a major effect of isoflurane on platelet activation while epidural anesthesia with ropivacaine provided better stability whether the liver was normal or compromised. De Rossi et al.[20] showed significantly higher expression of P-selectin on the surface of platelets with halothane and after 2 MAC isoflurane. In contrast, Dogan et al.[12] found that platelet aggregation was not significantly affected in patients anesthetized with isoflurane. Similar to the results of this study, Hussein et al.[21] revealed that patients with liver cirrhosis showed a significant increase in sP-selectin in comparison to controls. Increased sP-selectin levels in hepatitis C virus-related chronic hepatitis were suggested to be correlated with viral load and related to the degree of liver disease.[22]

On the other hand, the present study revealed that epidural anesthesia did not induce platelet activation as evidenced by trivial changes of sP-selectin levels. This agrees with Lo et al.,[23] who demonstrated that the clinically used local anesthetics; lidocaine, ropivacaine and bupivacaine seem to have only a limited ability to inhibit thromboxane A_2 (TxA_2)-induced platelet aggregation. Hollmann et al.[24] stated that the use of epidural anesthesia prevented immediate post-operative hypercoagulability without affecting physiologic aggregation and coagulation processes. However, there is evidence that local anesthetic *per se* affects aggregation as there was a significant correlation observed between bupivacaine plasma levels, incubation time, and the inhibition of all platelet aggregation variables.[25] In addition, local anesthetic blocks the Ca^{2+} uptake in platelets through selective inhibition of the Ca^{2+}-dependent adenosine triphosphatase.[26]

In this study, vWF activity increased significantly in all groups which was more pronounced in general anesthesia groups compared to epidural anesthesia. The same results were reported by Bredbacka et al.[27] These findings indicate that general anesthesia exerts a more adverse effect on endothelial cells. Chronic liver diseases were also associated with the high plasma levels of vWF. This could be due to endothelial shear stress related to portal hypertension. A correlation between severity of liver disease and vWF plasma antigen levels has been documented.[28]

Bruckner *et al.*[17] reported a non-significant increase in PF_{1+2} between general and regional group until 24 hours post-operatively which returned to the normal value on the fifth day. On the contrary, the present work revealed a significant increase in general anesthesia subgroups immediately and on the third post-operative day indicating its adverse stimulatory effect on blood coagulation.

On the other hand, the present study showed that tPA, PAI-1 and D-dimer were significantly high preoperatively in hepatic patients compared to control cases which may be due to decreased hepatic clearance. The inhibitor (PAI-1) concentrations are insufficient to counteract the increase in tPA, accounting for increased fibrinolysis as reported by Hersch *et al.*[29] Hyperfibrinolysis is correlated with the severity of liver dysfunction in cirrhosis, as assessed by Child–Pugh score and documented in many studies.[30,31] In a study conducted by Modig et al.,[32] they showed that the resting concentration of plasminogen activator decreased significantly and fibrinolysis inhibition activity increased significantly on the third day after operation with general anesthesia (opioid based with nitrous oxide) than extradural anesthesia (used bupivacaine). Wang et al.[33] concluded that epidural bupivacaine anesthesia can preserve fibrinolytic function after lower abdominal surgery by the inhibitory effects on surgical stress and PAI-1. The lower abdominal surgical procedures included in this study were classified as moderate and low-risk procedures in cases with chronic hepatic diseases.[34] The two anesthetic techniques used in this study did not result in any post-operative complications in patients with chronic liver disease.

The present study showed that D-dimer levels increased significantly during the post-operative period in patients anesthetized generally by isoflurane compared to patients anesthetized by epidural ropivacaine. This indicates better balance between coagulation and fibrinolysis with epidural ropivacaine anesthesia especially in hepatic patients complaining of already existing coagulation derangements.

Conflicting results were observed between studies which compared the effect of general and regional (whether epidural or spinal) anesthesia on D-dimer level. Bruckner et al.[17] revealed similar intraoperative course in both types of anesthesia that reached a peak level at 24 hours post-operatively and remained elevated until the fifth post-operative day. On the other hand, Rosenfeld et al.[35] and Sharrock et al.[36] reported no significant changes over time in both general and regional anesthesia. However, patients in Rosenfeld study underwent vascular surgery (elective lower extremity vascular reconstruction) in which tissue trauma was less than in Bruckner *et al.* and Sharrock *et al.* studies in which patients had undergone total hip and total knee arthroplasty respectively. In another study conducted by Siemens et al.,[37] they found that patients undergoing subtotal thyroid resection or laparoscopic cholecystectomy under general anesthesia showed significantly elevated D-dimer levels compared with normal values. These types of surgery definitely cause less tissue trauma than does vascular repair surgery. These conflicting results can be related to different sensitivity of test kits used, duration and type of surgical procedure, type of anesthetic drugs and techniques, and variables for estimating fibrinolytic activity.

The aforementioned studies demonstrated, first, that epidural anesthesia enhances fibrinolytic activity by preventing the post-operative release of plasminogen activator inhibitor-1 protein;[35] second, a larger baseline concentration of plasminogen activators; and an increased capacity of the venous endothelium to release plasminogen activators.[32] All of these studies suggested that the epidural administration of local anesthetic is able to reverse, or at least limit, perioperative hypercoagulability by preventing the release of procoagulatory mediators, by inhibiting their signalling pathways, or through increased fibrinolysis. The association of epidural anesthesia and analgesia with reduced post-operative stress responses may be the cause of platelet activity attenuation post-operatively.[38] In the present study, no biochemical markers of the stress response were measured. However, previous studies demonstrated that the decrease in cortisol, renin, aldosterone, and catecholamine levels had been associated with epidural anesthesia and analgesia, especially when used for procedures involving the abdomen and lower extremities.[32,39]

Conclusion

This study concluded that there was a significant post-operative decrease in hemoglobin level and a mild post-operative increase in the platelet count but within a clinically acceptable range. Post-operative changes of PT, PTT and TT were almost comparable between general and epidural anesthesia. General anesthesia using isoflurane showed a significant marked increase in hemostatic and fibrinolytic markers (sP-selectin, vWF, PF_{1+2}, tPA, PAI-1 and D-dimer) when compared to epidural anesthesia with ropivacaine whether the liver was normal or compromised. Epidural anesthesia using ropivacaine provided better stability on hemostatic system so it is recommended to be used in hepatic patients. If there is contraindication to perform regional technique, general anesthesia with isoflurane can be used safely since all the hematological changes are considered transient and reversible. Larger scale studies with extended follow-up are recommended to confirm the results seen in our study and to allow better understanding of hematological alterations related to general and regional anesthesia during and after surgery in patients with liver dysfunction.

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