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Abstract

Background: During hepatectomy, intermittent portal triad clamping reduces ischemia-reperfusion injuries. Pharmacological preconditioning with sevoflurane revealed similar properties. The aim of the study was to evaluate the combination of a preconditioning with sevoflurane with intermittent portal clamping on ischemia-reperfusion injuries.

Methods: Three regimens of anesthesia were applied: group SEV with continuous application of sevoflurane, group PRO with continuous propofol infusion and group PC where continuous propofol was substituted by sevoflurane (adjusted to reach MAC*1.5) for 15 minutes before intermittent clamping. Endpoints were the values of AST and ALT, factor V, prothrombin time, bilirubinemia over the 5-postoperative days (POD), morbidity and mortality at POD30 and POD90.

Results: The ALT values at POD5 were lower in the PC group (n = 27) 74 (48-98) IU/L compared to PRO (n = 26) and SEV (n = 67) respectively 110 (75-152) and 100 (64-168) IU/L (p = 0.038). The variation of factor V compared to preoperative values was less important in the PC and SEV groups respectively -14% and -16% vs -30% (PRO) (p = 0.047). Other criteria were not significant.

Discussion: Our study suggests that sevoflurane attenuates ischemia-reperfusion injuries on liver function, compared to propofol, without benefit for a specific regimen of pharmacological preconditioning when intermittent triad clamping is applied.

Introduction

Hepatic surgery is the standard treatment of several liver diseases, including malignant or benign tumors. Liver resection, especially when quite extensive, may be associated with major hemorrhage which affects short and long-term outcomes associated with blood transfusion (1). Therefore, techniques involving vascular control have been devised such as inflow vascular occlusion (portal triad clamping or Pringle's maneuver) or both liver inflow and outflow (total hepatic vascular occlusion) (2, 3). However, the aforementioned technics are associated with ischemic-reperfusion (IR) injuries, which can diminish the ability of the remnant liver to maintain its post-operative function. Two protective strategies against tissue damage due to ischemia have been suggested namely intermittent clamping triad and ischemic preconditioning.

Intermittent portal triad clamping is described as cycles of intermittent clamping for 15 minutes of ischemia followed by reperfusion for 5 minutes (4). Compared to continuous clamping, intermittent clamping causes less ischemic-reperfusion injuries (5, 6). Ischemic preconditioning is usually performed before starting liver transection and consists of 10 minutes inflow occlusion followed by 10 minutes of reperfusion period before a prolonged inflow vascular occlusion. However, recent meta-analysis failed to find significant benefit for liver resection compared to intermittent clamping (7).

Several medications have been propounded for pharmacological liver preconditioning such as volatile anesthetic agents. Halogenated anesthetic agents mimic ischemic preconditioning effects (8-12). In both cases, several pathways are involved: decreasing of reactive oxygen species production, decreasing lipid peroxidation inside liver parenchyma, up-regulation of inducible nitric oxide synthase expression, protein kinase C pathway, and opening of mitochondrial ATP sensitive potassium channels (mitoKATP) (13, 14). All these mechanisms contribute to reduce IR injury in heart ischemia and cerebral ischemia models (10, 14, 15).

In a clinical trial in 2008, Beck-Schimmer et al. reported that preconditioning with sevoflurane, a volatile anesthetic agent, for 30 minutes before inflow hepatic occlusion would reduce perioperative hepatocytes injuries reflected by a postoperative liver enzymes decrease and a postoperative morbidity decrease. However, permanent triad clamping was applied during surgery (16). Today, in our surgical ward, surgical technique consists in intermittent triad portal clamping rather than ischemic preconditioning (7).

The objective of our study was to evaluate whether pharmacological preconditioning with sevoflurane in patients undergoing hepatic surgery with intermittent portal triad clamping may attenuate ischemic-reperfusion injury and improve postoperative hepatic function.

Materials and Methods

Study design and patients

This study is a retrospective analysis extracted from a prospective liver surgery database. We included consecutive patients undergoing any kind of liver resection with intermittent portal triad occlusion for benign or malignant diseases between March 2013 and August 2014. Exclusion criteria were: age below 18 years old, emergency situations where hepatic inflow occlusion cannot be proceeded by pharmacological preconditioning, total vascular exclusion, and need for extracorporeal circulation.

According to local ethics committee, written informed patient consent was obtained from all participants for registration in database (e-LOGINSERM® HpbChir V3s © 2011) and data utilization.

Anesthesia

All patients received oral midazolam (0.1 $mg.kg^{-1}$) as premedication. Before general anesthesia, all patients received 200 µg of intrathecal morphine to improve postoperative analgesia. Anesthesia depth was assessed with entropy monitor (GE Healthcare®), which is a bispectral index (BIS) equivalent anaesthetic monitor as previously reported by our group (17). The same standardized anesthetic induction protocol was used to manage all patients included in the study: propofol (2–3 $mg.kg^{-1}$), sufentanil (0.5 $\mu g.kg^{-1}$), and atracurium (0.5 $mg.kg^{-1}$). Additional doses of sufentanil (0.3 $mg.kg^{-1}$) and atracrium (0.2 $mg.kg^{-1}$) were given if blood pressure or heart rate increased above 20% of preoperative value and to maintain neuromuscular blockade with a train of four below 40%. Conventional hemodynamic monitoring included electrocardiogram, pulse oximetry, continuous arterial pressure, and cardiac index, stroke volume variation (SVV) obtained with continuous pulse wave analysis device (Flo Trac/Vigileo®). Fluid restriction was applied for all patients (2 $mL.kg^{-1}$ per hour of crystalloids). If SVV rise up to 11%, additional fluids (250 mL of colloids) were administrated until return to normal value (18, 19, 20).

Therapeutic strategy aimed to maintain mean arterial pressure (MAP) up to 65 mmHg, and SVV < 11%. If MAP was under 65 mmHg, norepinephrine 0.2 to 0.5 $\mu g.kg^{-1}.min^{-1}$ was administrated. Intraoperative hemodynamic values and clinical events (arterial hypotension defined as MAP < 20%, arterial hypertension as MAP > 20% of preanesthetic values, tachycardia as a heart rate > 20% of preoperative value, and bradycardia as a heart rate < 50 $beats.min^{-1}$) were recorded. Blood transfusion was considered according to French National Authority for Health guidelines (21). Frozen fresh plasma was not use in our routine practice unless major bleeding.

After tracheal intubation, three regimens of anesthesia were applied aimed for a state entropy value of 40 in order to maintain a deep anesthesia over three periods of six months (Figure 1).

During the first period, group 1 (SEV), sevoflurane (end-tidal sevoflurane 1.2%-2.5%) was administrated. During the second period, group 2 (PC), target controlled infusion of propofol was administrated and preconditioning procedure was applied: 30 minutes before starting intermittent clamping, 1.5 MAC of sevoflurane was applied for 15 minutes followed by a 15 minutes washout (stopping sevoflurane administration, gas flow opened at 4 $L.min^{-1}$) then propofol was reintroduced. In the third group, group 3 (PRO), profopol was administrated as target-controlled infusion.

Surgical procedures

All cases were elective surgery. Type of surgery was noted, according to the international terminology (22): minor resection for < 3 segments, major resection for ≥ 3segments.

Surgical procedures were performed by an experienced surgeon. After liver mobilization, intermittent clamping was realized by the tourniquet around the portal triad with a Mersilene® tape. Intermittent clamping was repeated until total completion of hepatic transection. Clamping and unclamping durations were recorded.

Study endpoints

The primary endpoint was aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) peaks, which are usually used to define postoperative hepatocyte injury.

Additional endpoints were daily values of AST and ALT, factor V, prothrombin time (PT), bilirubinemia. A ratio of variation from preoperative factor V (fV) was calculated as (the minimum postoperative fV value – preoperative fV) / preoperative fV value. The same method was used to calculate the ratio of variation of prothrombin time and bilirubinemia. Albuminemia, glycemia, urea and creatinine plasma levels were also recorded. Morbidity was assessed by Clavien-Dindo classification (23), severe morbidity defined as a score ≥ IIIa, postoperative ascites formation defined as volume above 500 mL of ascitic fluid from abdominal drains, thoracic drains, or paracentesis, length of hospitalization, postoperative day (POD) 30 and POD90 mortality.

Data collection

Data were collected retrospectively. They were extracted from a database (e-LOGINSERM® HpbChir V3s © 2011 INSERM UMR_S 1136, IPLESP, Team EPAR, e-SQF and ACHBT) available on a secure website (http: //hpbchir.u707.jussieu.fr). Data had been filled in the database by clinical research assistants, members of the surgical team, and members of the anesthesiology team of Lille University Hospital. Missing data were supplemented through

the software available at Lille University Hospital: Diane® (anesthesiologic data), Cirus® (biological data), and Sillage® (medical data).

Statistical analysis

Quantitative parameters were described in terms of mean and standard deviation or median and interquartile ranges. Normality of distributions was checked graphically and using the Shapiro-Wilk test. Qualitative parameters were expressed as frequencies and percentages.

To compare our three groups of patients with quantitative variables, the Kruskal Wallis test or the analysis of variance was used according to the distribution of variables. For qualitative variables, the chi-square test (or Fisher exact when the theoretical numbers were less than 5) was achieved. To compare the different evaluation criteria between the three groups, the analyses were adjusted for the preoperative values of each criterion.

Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).

Results

Patient characteristics

One hundred and twenty-two patients were included, 2 patients were excluded because of extracorporeal circulation, 120 patients were analyzed. Patient characteristics are itemized in Table 1. There was no difference in demographic data and perioperative parameters within the three groups.

Peroperative data

Perioperative data are detailed in Table 2. The three groups were comparable, except for the use of vasopressors in the groups receiving propofol: group 2 (PC) 62 %, group 3 (PRO) 53%, group 1 (SEV) 10%, $p < 0.001$, and as expected the end-tidal sevoflurane concentration (mean (deviation)) between the group 2 (PC) 2.54% (+/-0.54) (= 1.5*MAC) and the group 1 (SEV) 1.34% (+/-0,42) (= 0.8*MAC), $p < 0.001$.

Endpoints

Postoperative data are shown in Table 3. AST and ALT values were not statistically different between the three groups, with a same trend: respectively lower in PC than in SEV than in PRO groups. The same trend was found regarding to AST and ALT daily values, and reached the statistical significance at POD5 for ALT (Figure 2).

The factor V ratio compared to preoperative values was less important in the groups with administration of sevoflurane: group 2 (PC) -14 [(-34)-(+6)] %, group 1 (SEV) -16 [(-41)-(+4)] %, group 3 (PRO) -30 [(-38)-(-22)] %, p= 0.047.

Regarding to bilirubinemia, albuminemia, glycemia, urea and creatinine plasma levels, there was no statistical difference between the three groups. Morbidity, severe morbidity, length of hospitalization and mortality at POD30 and POD90 were not significant too (Table 4).

A post-hoc subgroup analysis was performed in patients with major hepatectomy (n=46) and in patients with high risk of postoperative liver failure (n=94) (major hepatectomy or cirrhosis history (n=15) or preoperative chemotherapy (n=63)). In patients with major hepatectomy, although postoperative AST and ALT values were higher than in our global population, there was the same trends between the three groups: PC better than SEV better than PRO, but without significance. The variation of factor V was higher too, with similar respective trends between the three groups. In patients with high risk of postoperative liver failure, same results were found, and POD5 ALT values reached the significance. Among our global population, 13 postoperative ascites formation occurred in the 105 non-cirrhotic patients, and 7 in the 15 cirrhotic patients (5 in SEV, 2 in PRO groups).

In cirrhotic subgroups, the detail of severe morbidity was: in group 1: 1 pneumonia with septic shock, 1 biliary fistula ; in group 2: 1 abdominal hemorrhage requiring radiologic embolization, 1 pneumonia with septic shock ; in group 3: 1 intraperitoneal abscess.

Discussion

Outcomes

In our study there were no significant differences in postoperative liver injury as reflected by transaminase peaks between the three groups though trend lower values in groups SEV and PC. These results might suggest that pharmacological preconditioning with sevoflurane do not provide additional benefit when intermittent triad clamping is applied.

Plasma transaminase levels had been measured after liver surgery as markers of hepatocellular injury and have been used as endpoints in several randomized controlled trials (4-6, 16, 24). However, transaminase levels determined in peripheral blood might not adequately represent real hepatocellular injury as much as elevated levels might have multifactorial causes and are not associated with postoperative outcomes (25). Furthermore, transaminase levels did not correlate with the intra-operatively applied duration of vascular inflow occlusion, but rather with operative duration. Liver manipulation during surgical preparation is likely to promote cell death, inflammation, and liver dysfunction (26, 27). These findings introduced some uncertainty regarding clinical validity of plasma transaminase levels in liver resection. For these reasons, we preferred to evaluate the effect of preconditioning on liver synthetic and excretory function reflected respectively by prothrombin time (PT) and bilirubinemia.

Changes and mainly decreases in conventional markers of coagulation and clotting factors such as PT or INR, and factor V are common after hepatectomy and correlate with the extent of resection. Furthermore, consumption of clotting factors and decreased remnant liver synthetic function participate, as result of liver damage, in this deterioration. No patient in our study received fresh frozen plasma, increase in PT and factor V was related in an improvement of liver synthetic function. Patient's preoperative value, before IR injury was considered as reference.

Prothrombin time is a liver function marker. It depends on several factors, including factor V, synthetized by the liver. It is considered as a synthetic marker of remnant liver (28-30). Because preoperative factor V values were trendily favors preconditioning group, we decided to analyze not the absolute values, but the ratio of variation of minimum values on preoperative ones. By the way, our study is the first one which found a beneficial effect of sevoflurane on factor V after liver resection. This hypothesis should be supported by more clinical studies. Otherwise, factor V also increases in case of inflammatory response (31). We performed a post-hoc analysis and found no difference on postoperative sepsis occurrence between the three groups.

The main feared complication of ischemic-reperfusion injury is post-hepatectomy liver failure (PHLF). The definition of PHLF widely varied among studies. The most used are the "50-50" (PT <50% and bilirubinemia > 50µmol/L at POD5) (28) and the ISGLS's one (International

Study of Liver Surgery Group) (29). Three patients in the whole study developed PHLF (2 in SEV group and 1 in PRO group) ; 2 were cirrhotic patients, and 1 was not.

In our study, severe morbidity was 26%, mortality at POD30 was 1.6% and mortality at POD90 was 4.1%. A retrospective analysis of 1,500 consecutive patients undergoing hepatectomy found similar rates: 22.5% morbidity and hospital mortality of 3% (32). Cirrhotic patients (n=375) had higher morbidity (27.7% vs 20.7% in non-cirrhotic patients). Among complications, were observed: 61 cases of transient liver failure (4.1%), 56 of bile leakage (3.7%), 20 of abdominal bleeding requiring reoperation (1.3%), 15 of infection requiring reoperation (1.0%), 130 of symptomatic ascites (8.7%), 97 of pleural effusion (6.5%), 41 of subphrenic abscess (2.7%), 27 of transient renal insufficiency (1.8%), 14 of pneumonia (1.4%), 8 of small bowel occlusion (0.5%), 11 of sepsis (0.7%), and 5 of gastrointestinal bleeding (0.3%). Transient liver failure occurred in 7.1% in cirrhotic patients vs 3.0% in non-cirrhotic patients. Mortality was higher in cirrhotic patients (5.3% vs 2.2% in non-cirrhotic patients).

Our work did not find any difference in morbidity between the groups, unlike the Beck-Schimmer et al.'s one (16): severe morbidity of 6.7% in the preconditioning group against 26.5% in the propofol group ($p = 0.05$). Patients in this study received continuous clamping, and history of cirrhosis were excluded. Nowadays we know that continuous clamping causes more ischemia-reperfusion injuries than intermittent clamping (5, 6), and no difference in morbidity in our study could be explained by the beneficial effect of intermittent clamping.

Intraoperative use of norepinephrine was much more frequent in patients with propofol (with and without preconditioning). Although MAP was preserved, norepinephrine might decrease hepatic blood flow (33, 34). Interestingly, in the PC group, norepinephrine use was as frequent as in PRO group, but the consequences seem attenuated, perhaps due to sevoflurane impregnation.

Differences between group 1 and group 2

In our study, sevoflurane was conducted in two different ways: as pretreatment in PC group and as maintenance for anesthesia for SEV group.

The PC group received higher volatile halogenated agents than the SEV group. A dose-effect of pharmacological preconditioning is uncertain (14, 35-38). Obal et al. reported in a rat heart model that pharmacological preconditioning with sevoflurane with an amount of 1 MAC provides more protection from IR cardiac injury than 0.75, but increasing the dosage beyond 1.0*MAC is useless (37). This phenomenon is called threshold effect. Length exposure to volatile halogenated agents would play a role too (39). There are not enough data concerning

the optimal duration of pharmacological preconditioning to dispense. In our work, the two protocols differ by the dosage and duration.

Beck-Schimmer et al showed, in another study, a post ischemic conditioning effect with sevoflurane (i.e. applied after inflow hepatic occlusion) (40). In our study, a sevoflurane continuous application in SEV group might be considered as a combined pre and post conditioning, with a lower dosage than PC group. A cardiac surgery study comparing 4 anesthesiology protocols (propofol throughout the procedure, sevoflurane preconditioning, postconditioning with sevoflurane, sevoflurane throughout the procedure) showed a benefit when the sevoflurane was administered before, during and after reperfusion (41). This work suggests an additive effect of preconditioning and postconditioning. The molecular configuration of propofol, closed to vitamin E, confers on it antioxidant properties (42-44). When applied before ischemia, its antioxidant properties may attenuate pharmacological preconditioning effects.

Rodriguez *et al* found no benefit for volatile anesthetic preconditioning when intermittent inflow occlusion was applied (45). However, patients with underlying liver disease were excluded. Indeed, in cirrhotic patients, Yang *et al* results suggest that maintenance of anesthesia with isoflurane is associated with an attenuated postoperative inflammatory response and less postoperative hepatocellular injury compared with propofol, even if intermittent clamping is applied (46).

In our study, the 1.5*MAC sevoflurane preconditioning regimen seems not to provide benefit effect on liver injury when compared to sevoflurane for maintenance of anesthesia. However, it might be interesting in case of difficult scheduled resections, when difficult intermittent clamping is predicted and when continuous clamping would be applied because of liver local conditions.

Study limitations

Our study has limitations. First, due to a small sample size in our study, there was a lack of power to detect any effect of anesthesia regimen on morbidity. Second, this is a retrospective, non-randomized, single center study. Different protocols have been proposed over the time, in this following order: 1, 2, 3. We waited for consecutive patients belonging to the same group over the time. The historic protocol mainly practiced by all anesthetists was the SEV protocol. The Lille University Hospital includes many anesthesiologists, more or less specialized depending on the type of surgery. It happened sometimes that a non-specialist anesthesiologist in liver surgery handle a patient getting a liver resection surgery. The anesthesia protocol which was applied routinely was the SEV protocol.

Conclusion

In conclusion, our study suggests that sevoflurane attenuates the impact of ischemia-reperfusion injuries on liver function, compared to propofol, without benefit for a specific regimen of pharmacological preconditioning at MAC*1.5 sevoflurane when intermittent triad clamping is applied.

Conflicts of interest

None declared.

Figure 1: Treatment protocols for the three groups; MAC: minimum alveolar concentration; FEt: end-tidal sevoflurane (%) in mean (deviation).

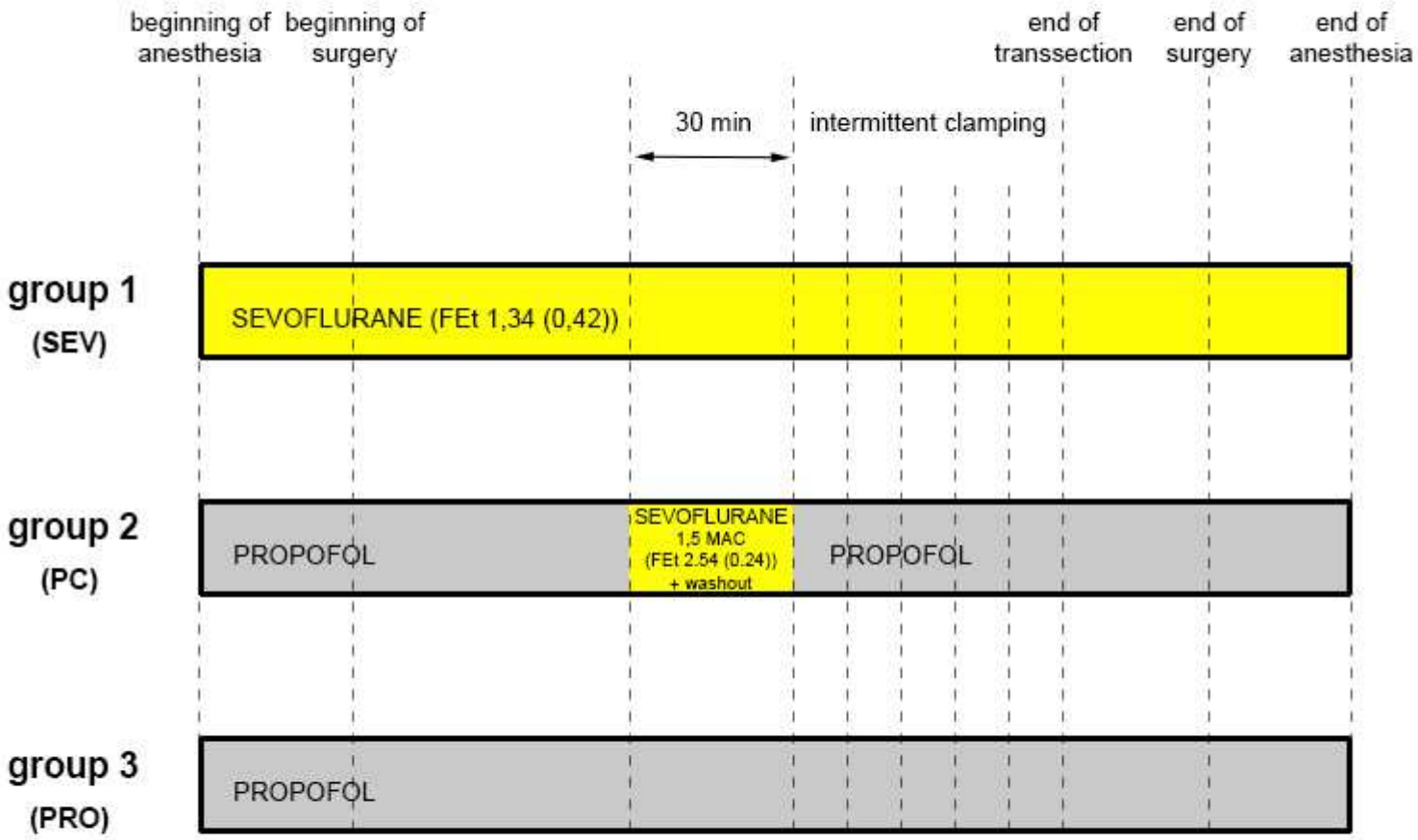

Table 1: Patient characteristics at baseline; BMI: body mass index; preop: preoperative; AST: aspartate-aminotransferase; ALT: alanine-aminotransferase; PT: prothrombin time.

	group 2 (PC)	group 1 (SEV)	group 3 (PRO)	p value
	(n=27)	(n=67)	(n=26)	
Age, years, median (range)	65 (57-68)	61 (51-67)	63 (53-68)	0.38
Female, n (%)	10 (37)	33 (49)	11 (42)	0.53
BMI, kg/m², median (range)	23 (21-28)	24 (22-29)	25 (23-29)	0.13
Diabetic, n (%)	3 (11)	9 (13)	4 (15)	0.87
Cirrhotic, n (%)	2 (7)	10 (14)	3 (11)	0.65
Carcinologic surgery, n (%)	25 (92)	61 (91)	23 (88)	0.83
Indication:				
Benign lesions, n (%)	2 (7)	6 (8)	3 (11)	-
Hepatocellular carcinoma (%)	7 (26)	13 (19)	4 (15)	-
Cholangiocellular carcinoma (%)	3 (11)	7 (10)	2 (7)	-
Colorectal cancer metastasis (%)	13 (48)	35 (52)	12 (46)	-
Non colorectal cancer metastasis (%)	1 (4)	4 (6)	1 (3)	-
Other malignant lesions (%)	1 (4)	2 (3)	4 (15)	-
Rehepatectomy, n (%)	6 (22)	14 (20)	8 (30)	0.59
Preop AST, UI/L, median (range)	28 (20-60)	26 (19-38)	29 (22-34)	0.35
Preop ALT, UI/L, median (range)	30 (20-49)	22 (16-37)	29 (19-37)	0.14
Preop factor V, %, median (range)	140 (113-169)	114 (97-144)	125 (105-162)	0.08
Preop PT, %, median (range)	100 (94-100)	95 (86-100)	92 (87-100)	0.058
Preop bilirubinemia, µmol/L, median (range)	8 (5-13)	8 (5-10)	8 (5-11)	0.77
Preop albuminemia, g/L, median (range)	40 (38-42)	42 (38-45)	42 (36-43)	0.41
Preop glycemia, mmol/L, median (range)	4.5 (4.0-6.5)	5.0 (4.0-6.0)	4.0 (4.0-6.0)	0.50
Preop urea, mmol/L, median (range)	5 (4-6)	5 (4-6)	5 (4-6)	0.96
Preop creatinin (µmol/L), median (range)	70 (62-82)	75 (68-88)	70 (60-79)	0.23

Table 2: Peroperative data; RBC: red blood cells; FEtSev: end-tidal sevoflurane concentration; *: significant between the 3 groups; Ł: significant between the group 2 and the group 1.

	groupe 2 (PC)	groupe 1 (SEV)	groupe 3 (PRO)	p value
	(n=27)	(n=67)	(n=26)	
Major hepatectomy, n (%)	14 (51)	24 (35)	8 (30)	0.23
Number of clamping, median (range)	2 (1-3)	3 (2-4)	2 (2-4)	0.08
Total duration of ischemia, min, median (range)	37 (16-44)	40 (27-61)	33 (23-50)	0.06
Blood loss, mL, median (range)	400 (300-700)	400 (200-800)	500 (300-800)	0.55
RBC transfusion, n (%)	2 (7)	13 (19)	4 (15)	0.39
Volume expansion (mL), median (range)	2500 (2000-3080)	2500 (2000-3000)	2875 (2000-3250)	0.43
Vasopressors, n (%)	17 (62)	7 (10)	14 (53)	<0.001 *
MAP < 60 mmHg (min), median (range)	7.0 (1.6-14.3)	5.8 (1.2-17.7)	4.0 (1.1-9.9)	0.80
MAP < 65 mmHg (min), median (range)	12.1 (4.8-35.4)	19.3 (6.3-39.2)	10.2 (2.1-30.1)	0.67
FEtSev (%), mean (deviation)	2.54 (0.24)	1.34 (0.42)	0	<0.001 Ł
Duration of general anesthesia (min), median (range)	374 (318-473)	365 (301-441)	374 (319-444)	0.76

Figure 2: Daily values of alanine-aminotransferase (ALT); preop: preoperative; *: significant between the 3 groups.

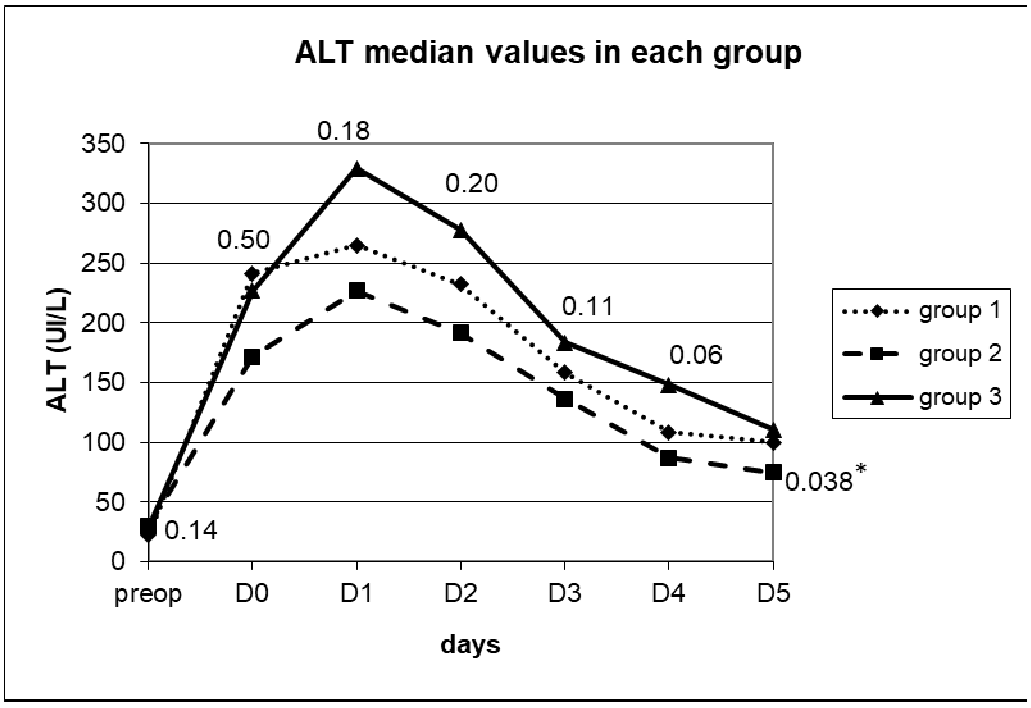

Table 3: Postoperative data; preop: preoperative; POD: postoperative day; AST: aspartate-aminotransferase; ALT: alanine-aminotransferase; fV: factor V; Pct_minfV = (minimum fV – preoperative fV) / preoperative fV; PT: prothrombin time; Pct_minPT = (minimum PT – preoperative PT) / preoperative PT; Pct_MaxBili = (Maximum bilirubinemia – preoperative bilirubinemia) / preoperative bilirubinemia; *: significant between the 3 groups.

		groupe 2 (PC)	groupe 1 (SEV)	groupe 3 (PRO)	p value
		(n=27)	(n=67)	(n=26)	
AST (UI/L), median (range)	preop	28 (20-60)	26 (19-38)	29 (22-34)	0.35
	POD0	247 (189-367)	257 (153-469)	315 (210-397)	0.45
	POD1	214 (152-388)	265 (150-457)	346 (218-563)	0.16
	POD2	122 (95-217)	174 (101-308)	237 (123-384)	0.17
	POD3	76 (53-99)	82 (54-140)	95 (64-135)	0.33
	POD4	53 (42-61)	52 (38-90)	63 (52-85)	0.23
	POD5	52 (38-60)	50 (39-69)	46 (37-56)	0.69
Peak of AST (UI/L), median (range)		254 (198-438)	294 (153-559)	389 (275-570)	0.18
ALT (UI/L), median (range)	preop	30 (20-49)	22 (16-37)	29 (19-37)	0.14
	POD0	171 (121-333)	241 (139-360)	227 (152-354)	0.50
	POD1	227 (123-370)	265 (154-457)	329 (219-455)	0.18
	POD2	191 (108-292)	232 (134-448)	277 (172-418)	0.20
	POD3	136 (74-163)	158 (92-300)	183 (122-268)	0.11
	POD4	87 (53-150)	108 (67-205)	148 (115-225)	0.06
	POD5	74 (48-98)	100 (64-168)	110 (75-152)	0.038 *
Peak of ALT (UI/L), median (range)		261 (141-372)	292 (159-509)	344 (264-602)	0.14
Pct_minfV (%), median (range)		-14 [(-34)-(+6)]	-16 [(-41)-(+4)]	-30 [(-38)-(-22)]	0.047 *
Pct_minPT (%), median (range)		-33 [(-40)-(-18)]	-26 [(-38)-(-16)]	-22 [(-33)-(-15)]	0.57
Pct_MaxBili (%), median (range)		+164 [(+34)-(+494)]	+142 [(+61)-(+267)]	+118 [(+70)-(+283)]	0.99

Table 4: Morbidity and mortality. POD: postoperative day.

	groupe 2 (PC)	groupe 1 (SEV)	groupe 3 (PRO)	p value
	(n=27)	(n=67)	(n=26)	
Morbidity (Clavien-Dindo score), median (range)	2 (1-3b)	2 (1-3a)	2 (1-2)	0.54
Severe morbidity (n ; %)	9 ; 33	17 ; 25	6 ; 23	0.13
Complication (n ; %)				
Post-hepatectomy liver failure	0 ; 0	2 ; 2.9	1 ; 3.8	-
Biliary fistula	0 ; 0	3 ; 4.4	1 ; 3.8	-
Ascites	2 ; 7.4	13 ; 19.40	5 ; 19.23	0.40
Blood effusion or collection	2 ; 7.4	0 ; 0	1 ; 3.8	-
Pleural effusion	3 ; 11.1	5 ; 7.4	1 ; 3.8	-
Atelectasia	0 ; 0	1 ; 1.4	1 ; 3.8	-
Pneumonia	2 ; 7.4	2 ; 2.9	1 ; 3.8	-
Pneumothorax	1 ; 3.7	2 ; 2.9	0 ; 0	-
Urinary infection	2 ; 7.4	2 ; 2.9	1 ; 3.8	-
Intraperitoneal abscess	1 ; 3.7	4 ; 5.9	2 ; 7.6	-
Acute kidney injury	1 ; 3.7	1 ; 1.4	1 ; 3.8	-
Delirium	2 ; 7.4	0 ; 0	2 ; 7.6	-
Sepsis	8 ; 29.6	25 ; 37.3	9 ; 34.6	0.56
Other	3 ; 11.1	3 ; 4.4	1 ; 3.8	-
Length of hospitalisation (days), median (range)	10 (8-14)	9 (7-13)	8.5 (7-14)	0.33
Mortality at POD30 (n ; %)	0 ; 0	1 ; 1.49	1 ; 3.85	-
Mortality at POD90 (n ; %)	1 ; 3.70	3 ; 4.48	1 ; 3.85	-

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