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PARTIAL PORTAL VEIN ARTERIALIZATION MAINTAINS REGENERATION AFTER CRITICAL MAJOR HEPATECTOMY: EXPERIMENTAL STUDY

By

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Abstract

Portal vein arterialization (PVA) is often referred to as a salvage procedure for insufficient arterial or portal inflow. Its main role focuses on two domains, liver transplantation and extensive surgery for malignancies of liver, biliary tract and pancreas. It has been applied in treatment of fulminant hepatic failure due to intoxications and as a bridging procedure for transplantation or re-transplant. Radical resections with arterial reconstruction are a major challenge for surgeons especially in prolonging survival in advanced malignancies of the liver or biliary tract. This study revisited the benefits of this procedure to test the hypothesis of supporting a failing liver during critical period of regeneration following major hepatectomy with insufficient arterial inflow. The endpoints were to identify the histopathological and biochemical evidence of regeneration.

The experimental design: 24 adult dogs of both sexes were included. They were divided into 3 groups: G1 (n=7): animals subjected to 65% hepatectomy (control), G2 (n= 8): animals subjected to 65% hepatectomy & hepatic artery ligation, G3 (n=8): animals subjected to 65% hepatectomy & partial portal vein arterialization (PPVA). Blood samples were taken for assessment of liver functions and blood gas analysis. Liver biopsy was assessed for morphological and histopathological changes of regeneration. Gross specimens were used to calculate the liver regeneration rate.

Results showed the presence of mitotic activity and regeneration in groups with PPVA comparable to controls. No evidence of regeneration observed in G2. Shunt patency was confirmed by increase in PO2 levels of arterialized portal vein. A significant increase in the regeneration rate in groups with arterialized portal vein 1 week post procedure was noted.

Key words: Experimental study, Dog, Portal vein arterialization

Introduction

Portal vein arterialization (PVA) was historically used in portal hypertension surgery in conjunction with end-to-side portacaval shunting with the purpose of preserving liver perfusion and reducing the risk of hepatic failure and encephalopathy. However, despite precautions to optimize flow into the intrahepatic portal bed, complications were not uncommon. With time, this approach was abandoned and alternative radiological shunting therapies were adopted in favour of the former (Otte *et al*, 1982). Temporary use of portal arterializations during liver transplantation surgery has shown beneficial effects on shortening warm ischemia time of the donor liver and consequently reducing the Incidence of immediate postoperative graft failure (Morimoto *et al*, 1992). Out of transplantation domain, PVA has been performed to prevent hepatic artery thrombosis (HAT) after extensive cancer surgery and in fulminant hepatic failure due to intoxications (Qiu *et al*, 2012).

The surgical literature cites the incidence of liver failure after hepatectomy to be dependent on the capacity for regeneration of the remnant liver mass; which in turn is also dependent on a steady supply of energy, mainly by mitochondrial respiratory chain which consumes about 90% of the oxygen utilized by the liver .However, under critical conditions; hepatocytes may have an oxygen concentration at which mitochondrial respiration and ATP synthesis are partially oxygen limited. The capacity of regenerating

hepatocytes is further compromised under these conditions as the liver's unique blood supply is 80% de-oxygenated blood via portal vein. Hypothetically, high oxygen saturation in the portal blood flow seems to improve the oxidative metabolism within the hepatocytes, thereby supporting the energy-dependent processes of regeneration through an increased production of ATP (Nonami *et al*, 1991).

This study tested the hypothesis of an augmented oxygen supply to the portal vein, by creating a controlled flow fistula, and the reflections of such changes on liver regeneration using large animal models, the morphological and pathological parameters of regeneration under critical conditions. The animals were exposed to a second laparotomy 1 week post initial procedure as this was speculated to be the peak phase of regeneration in dogs.

Materials and Methods

The present study was done in the experimental unit of Theodor Bilharz Research Institute (TBRI) and the Cairo University Hospital Experimental Labs. A total of 24 adult dogs of both sexes were included in the study ranging in weight from 10kg and 27kg. Dogs were housed in cages located in the facility and supplied with suitable diet. A dose of antibiotic veterinary pan-terramycin IM was given at induction both at the initial and 2nd laparotomy plus a STAT dose of a broad spectrum antiparasitic (0.1 mg/kg) SC. Weight and blood samples and liver biopsy were also taken to determine biochemical and histopathological markers of regeneration. Ethical committee approval was granted prior to commencing the study (TBRI).

Animals were randomly divided into three groups: G1 (control) a hilar 65% resection was performed to induce regeneration. In G2 65% partial hepatectomy with ligation of the hepatic artery was performed. G3 had 65% hilar resection + ligation of hepatic artery (HA) and partial portal vein arterialisation. All animals were subjected to two laparotomies. Blood samples were taken for analy sis:1- biochemical analysis: Albumin, AST, ALT and total bilirubin, 2- blood gas analysis (for G3). Liver biopsy was taken as base line before the procedure and further specimens were sampled at the 2nd laparotomy.

Anesthesia: Dogs were relaxed by Ketamine in a dose of 10 ml/kg with Atropine 0.1ml/5kg animal weight, in order to facilitate handling of the animal. After induction and intubation, maintenance propofol drip at a dose of 12ml/kg.hr in 500ml Dextran 5% was given as an infusion and ventilation with oxygen 8 liters/hour. Antibiotic (Veterinary Panterramycine) in a dose of 2.5 ml/10kg body weight was given IM with induction of anesthesia. Local anaesthesia (10 ml subcutaneous Xylocaine) was injected along midline wound at the end of procedure.

Dogs were positioned supine followed by shaving of midline. After a midline laparotomy incision, the porta hepatis was exposed following mobilisation of triangular ligament of liver. A window was made in the hepatoduodenal ligament, adjacent to the left lateral lobar portal vein at the base of the left lateral liver lobe, to isolate, ligate, and divide the left lateral lobar hepatic artery and left lateral lobar hepato-biliary duct. Hilar dissection for individual lobes of liver was done, subsequently ligating the lobar vein, artery and duct .The left medial, lateral and central lobes were removed paying attention to hemostasis. Cholecystectomy was done prior to dissecting the central division. A control 65% hepatectomy was achieved by leaving the right lateral (20%) caudate and papillary process (15%). The following figures show the steps of the procedure:

For G3 partial portal vein arterialization (PPVA) was completed creating a side-side splenic arterio-venous shunt. This was created using the diameter of the hepatic artery as the stoma (5-6.5mm). A bolus of 2000IU of diluted heparin in 10ml saline was injected intravenously followed by splenectomy. Blood samples for blood gas analysis were taken from the portal vein. The midline wound was closed using prolene 0 (mass

closure). Skin was closed with a subcuticular vicryl 2/0. The animal was housed under identically controlled environmental conditions. Water was permitted immediately post operatively. Free diet was permitted in the first day post operatively. A week post operatively, laparotomy through the previous incision was done. For G3, blood samples were taken for blood gas analysis (PO2 levels) was taken. Remnant liver tissue was used to calculate the liver regeneration rate. Hilar dissected was performed to resect the right medial, papillary and caudate process of remnant liver. Care was taken to repair the IVC as the same dogs were kept ventilated for other procedures as part of surgical skills workshops.

The estimated regeneration percentage of liver was calculated: Estimated weight of remnant liver at operation = W×35, where W = Weight of hepatic resection. This, subtracted from the weight of the liver removed at time of sacrifice, gave an estimate of the gain in liver weight during the experimental period. The gain divided by the weight of liver removed at operation was multiplied by 100 to express regeneration in percent.

All biopsy specimens were fixed in 10% buffered formalin solution for 12 hours processed in ascending grades of ethyl alcohol (70%, 90% & 100%), xylene and embedded into paraffin blocks. Five µm thick tissue sections were cut and stained with 1- Hematoxylin and Eosin stain 2. Masson Trichome stain for tissue fibrosis and demonstration of blood vessels in tissue sections. Hepatocyte injury was identified by a- Hydropic changes, ballooning degeneration, quantified (Suzuki and Toledo-Pereyra, 1993) from mild to marked, b- Steatotic changes (fatty degeneration) which was scored (Brunt *et al*, 1999) minimal (<10%) to diffuse (>70%).C) Necrosis and Apoptosis (<10% to >15%). The portal fibrosis which was semi-quantitavely recorded as either absent or increased >75%.

Criteria of regeneration were identified by presence of mitotic activity: a- Thickened liver cell plates, b- Presence of binucleated hepatocytes and c- Portal angiogenesis in the form of proliferated vascular channels (neo vascularization).

Immunohistochemical staining for the proliferation associated nuclear factor NF kuppa B (P105): Formalin fixed, paraffin embeded hepatic tissue sections (4m in thickness) were stained for anti NF-KB P105 antibody which is a monoclonal antibody specific for P105 protein (Novocastra Lab. Ltd) by avidin-biotinperoxidase complex method as follow: after de-waxing, inactivating endogenous peroxidase activity and blocking cross-reactivity with normal serum, sections were incubated overnight at 4°C with a 1:20 solution of primary antibody. Location of primary antibody was achieved by subsequent application of a biotinylated anti-primary antibody, an avidin-biotin complex conjugated to horseradish peroxidase, and diaminobenzidin (NOVO-Castra Lab. Ltd). The slides were counterstained by hematoxylin. Negative controls were established by replacing the primary antibody with PBS and normal serum. Positivity was estimated as nuclear or cytoplasmic staining detecting proliferating hepatocytes in interphase and mitotic phases of cell cycle. By light microscopy, immunohistochemical positivity was recorded and semi-quantitated as proliferating % (+ve) cells in tissue section.

Statistical analysis: Data were expressed in mean ± SD (standard deviation). Significant differences between the same group and different groups were tested using Student's T test. P = < 0.05 was considered significant.

Results

Standard hilar dissection was completed in an average time of 2 hours. The creation of a shunt added an extra 30mins to the procedure. No major blood loss was encountered. All dogs recovered promptly from anesthesia. Three dogs of G2 showed delayed recovery 4-5 hours but were able to stand after that. However, 5 days after procedure these dogs were anorexic and appeared lethargic. They were re-explored day7 and remnant liver biopsied at time of autopsy showed ev-

idence of necrosis. Remnant liver was used for calculation of liver regeneration rate.

Liver function and morphology: G2 showed marked changes of all markers reflecting the severity of liver injury. Cholestatic liver damage was apparent with an increase in post-operative bilirubin levels with significant difference between G2 and control (p=0.0003), and G3 (p=0.0001) see chart 1. No significant difference between G1 & 3 (p=0.78). Also, ALT, AST showed a marked post-operative increase, with significant difference between G2 with G1 & 3 p=<0.05). Albumin (chart 2), as a marker of synthetic function of the liver was decreased in all groups, however a significant decrease post-operative was observed in G2 as compared to G1 (p=0.019) & G3 (p=0.004). No significant difference was seen between G1 & G3 (p=0.7) suggested maintenance of adequate synthetic function of liver post-operative.

G1 models showed variable degrees of ballooning and hydropic degeneration ranging from mild to moderate. G2 showed mainly moderate degenerative changes (Fig. 7) that extended to severe changes in one case. No changes observed in G3 (chart 3). Mild degrees of necrotic foci were observed in G1 that were 2-3%. More marked necrosis was observed in G2 (Fig. 8) as was the degree of apoptosis. No necrosis in G3. Mild to moderate degree of congestion was observed in G3 as compared to G1, where only mild degree was in one case. However, more pronounced and increased in G2. G3 had readily observed fibrosis ranged from mild to moderate post operatively (Fig. 9). This was only mildly observed in G1 & G2.

Regeneration: regenerating hepatocytes with evidence of mitotic activity, binucleation and thickened cord plates were observed in G1 & 3 (Fig. 10, 11). No attempts of regeneration observed in G2. A significant difference in the PO_2 levels was observed pre and post shunt (chart 4). This would ensure increased oxygen saturation and hence delivery of oxygenated blood through the portal vein. It is also an indication of a patent shunt. Expression of P105: PPVA stimulated hepatocytes proliferation in up to 75% of cells in G3. Variable degrees of positivity were in G1 reached up to 50% in 4 models (Figs. 12, 13), non in G2. The mean regeneration percentage was 41% ±18.22 for G1, whereas for G3 an increment of 70% ±16 was observed (chart 5). The results were significant (p= 0.007). No attempt of regeneration was recorded in G2.

Discussion

In order to mimic the clinical impact of enbloc extended hepatectomies with sacrifice of the hepatic artery, or situations of hepatic artery thrombosis post-transplant leading to acute liver failure, hepatic artery was ligated in G2 cases. There are certain advantages in PVA models. The splenic artery was not too thick and close to the splenic vein. Minimal dissection was required and a controlled flow fistula could be easily created as a side to side anastomosis. This would ensure diversion of oxygenated blood to the portal vein. Caliber of the artery was small and this would ensure a low flow to the portal vein. The hilum was left untouched which can be of potential benefit in reducing possibilities of technical difficulties in transplant surgery. Nardo *et al*. (2005) recommended using a small caliber artery to reduce the risk of post-operative portal hypertension in the short term allowing recovery of the liver fail. Cavallari *et al.* (2001) reported a patient whose liver graft had hepatic artery thrombosis (HAT) and massive necrosis. Rescue was afforded by an end-to-side anastomosis between the recipient hepatic artery and the graft PV. PPVA represented a bridge to elective re-transplantation, which was done four months later. Shimizu *et al.* (2004) reported a case of preoperative HAT in living-donor liver transplantation. Because arterial re-anastomosis was not possible, PVA was performed through an arteriovenous shunt in the mesenteric vascular branches. At 45 days later, occlusion of the shunt and the development of collateral vessels to the graft were radiological detected.

At 14 months after OLT the patient displayed normal hepatic function. In this study, hepatic artery ligation was reflected by severity of liver damage (G2), without the support of an oxygenated blood supply massive necrosis develops. The liver did not show any attempts at regeneration and hence elevated serum functions directly correlates with the commencement of liver failure in that particular group. It is worth noted that dogs reported in literature die mainly from overwhelming infection secondary to ischemia following ligation of the hepatic artery. The only reason could speculate that dogs survived one week period was that regular injection of intramuscular ampicillin which probably played a role in short term survival (Markowitz *et al*, 1949; Tanturi *et al*,1950). However, this was not a survival study and only aimed to detect changes in regeneration parameters. A similar study by Shimizu et al, reported a 92% 10 day survival following 85% hepatectomy with portal vein arterialization as compared to the group with hepatic artery ligation (Shimizu *et al*, 2000).

Elevation of all markers post operatively was underscored by significance difference between G2 and the others. The variable degrees of architectural changes were also observed in all groups. This was a short term observational period; one would expect normalization of liver functions on long term (Lange *et al*, 1997) with longer follow-up periods. Adamson *et al*. (1978) investigated livers in healthy dogs and found that if arterial blood flow in the portal vein was controlled within the normal range of the portal vein, histological damage to liver did not occur. This confirmed the result in G3 which didn't reveal pronounce changes of hydropic degeneration, steatosis or necrosis compared to controls. Over the long-term, authors have reported structural changes in the liver parenchyma after PVA. Necrotizing vasculitis, intimal fibrosis of the portal vein, and periportal fibrosis have been described (McCredie *et al*, 1957; Zuidema *et al*, 1963; Asakawa *et al*, 1985). The present study showed that both an appreciable increase in congestion and moderate degree of fibrosis were observed in G3 post-operative, as proliferating hepatocytes, maintained the capacity of the liver to regenerate and the global sinousiodal shape was not disturbed. This agreed with Fan *et al.* (2002) that when inflow rates were equivalent, hepatectomized livers with an arterialized portal supply could regain the weight as fast as those with a portal venous supply

The general condition of G3 in the 2nd laparotomy did not reveal any congestion of the intestine or dilatation of the portal vein. Chen *et al*. (2008) found that one month post PVA in rat models, where the hepatic artery was anastomosed to the distal portal vein. As to the hepatocyte proliferation; Nardo *et al*. (2005) found that hepatocyte proliferation, assessed by 5- bromo-2-deoxyuridine labeling and mitotic indices, was rapidly induced in rats treated with PVA at 24 hours after carbon tetrachloride intoxication, when extensive liver necrosis was already established. This finding was accompanied by a significant improvement in 10-day survival from 30% to 100% when compared with intoxicated, non-arterialized rats It's worth noting that their experiment did not involve ligation of the hepatic artery but rather an augmented oxygen supply via creation of PVA. G3 showed evidence of mitotic activity by detection of binuclated hepatocytes and thickened cord plates, but not in G2. So, it can speculate that not only did PVA triggers regeneration but able to maintain it even with interruption of the hepatic artery.

Different methods can be used to assess the liver regeneration such as the detection of liver weight, serum enzyme level, and immunohistochemistry for nuclear antigen (Assy *et al,* 1997; Fan *et al*, 2002; Schleimer *et al*, 2008). In this study, immunohistostaining P105 was used. Positivity was estimated as nuclear or cytoplasmic staining detecting proliferating hepatocytes in interphase and mitotic phases of cell cycle. The proliferating hepatocytes expressed higher positivity

as compared with the controls. This agreed with Zhang *et al.* (2011) using Ki69 and PCNA, and postulated that elevated pressure in the sinusoids associated with PVA was responsible for accelerated liver regeneration. This was found in the liver after PVA in a rat model (Ott *et al*, 2003). In the present study, up to 75% of hepatocytes showed high positivity as compared to controls. In analogy to this, accentuated angiogenesis were observed in groups with PPVA as compared to controls that were more in line with foregoing studies. Schleimer *et al*. (2008) detected the hepatocyte apoptosis using M30 Cytodeath immunohistochemistry. They showed that animals underwent PVA had post-operative day 2 ($P<0.01$); without significant difference in apoptotic cells number between two groups 4 days after surgery. The present results showed no changes in apoptotic cells number between G1 & G3 that differed from Schleimer *et al*. (2008). This might be attributed to different methods for apoptosis detection. TUNEL assay is high-specificity for apoptosis detection of (Loo *et al*, 2002; Costa *et al*, 2010). Zhang *et al*. (2011) found that the right renal artery was anastomosed to portal vein which declined the time of warm ischemia from 30 min to 10 min. Liver ischemia reperfusion injury was reduced and hepatocyte apoptosis improved that caused discrepancy in results between them and Schleimer *et al.* (2008). Otte *et al.* (2003) reported an initial increase in models with PVA but later decrease

In the present study, by immmunohistochemsitry there was neither ischemia-reperfusion injury to liver nor post-operative changes in PPVA group. This correlated with the ischemia degree and liver damage inflicted to G2 that showed apoptotic cells of more than 15% in prepared sections. Liver increased in weight as compared with remaining residual parenchyma after 65% reduction in control group was on average, 41%±18.22. In PPVA group, there was an increment of 70%±16 $p= 0.007$. This agreed with (Fan *et al*, 2002; Otte *et al*, 2003; Muller *et al*, 2004). Blood gas levels for PO2 were taken pre and a week post shunt. Significant increase in PO2 levels were in keeping with shunt patency and ensuring adequate oxygenation of portal vein $p= 0.003$, which agreed with Kazuaki *et al*. (1997) and Shimizu *et al*. (2000). High oxygen saturation in port blood flow improved oxidative metabolism within hepatocytes, thereby supporting energy dependent processes of regeneration under critical conditions.

Conclusion

The proper blood perfusion in portal tract is essential for initiating and maintaining liver regeneration after major and or critical partial hepatectomy. An equivalent inflow rate, the immediate hepatic regeneration response can be initiated, and the 1-week liver regeneration rate can be sustained by an arterialized portal supply at same level as by a portal venous inflow, and should be regarded as an efficient salvage procedure for poor arterial or portal hepatic flow. Augmented portal oxygen supply gave beneficial effects on hepatic energy metabolism and liver regeneration, and led to improved survival after critical hepatectomy.

Recommendation

The strict surveillance is advised in selected cases to limit the potential onset of portal hypertension in the long term.

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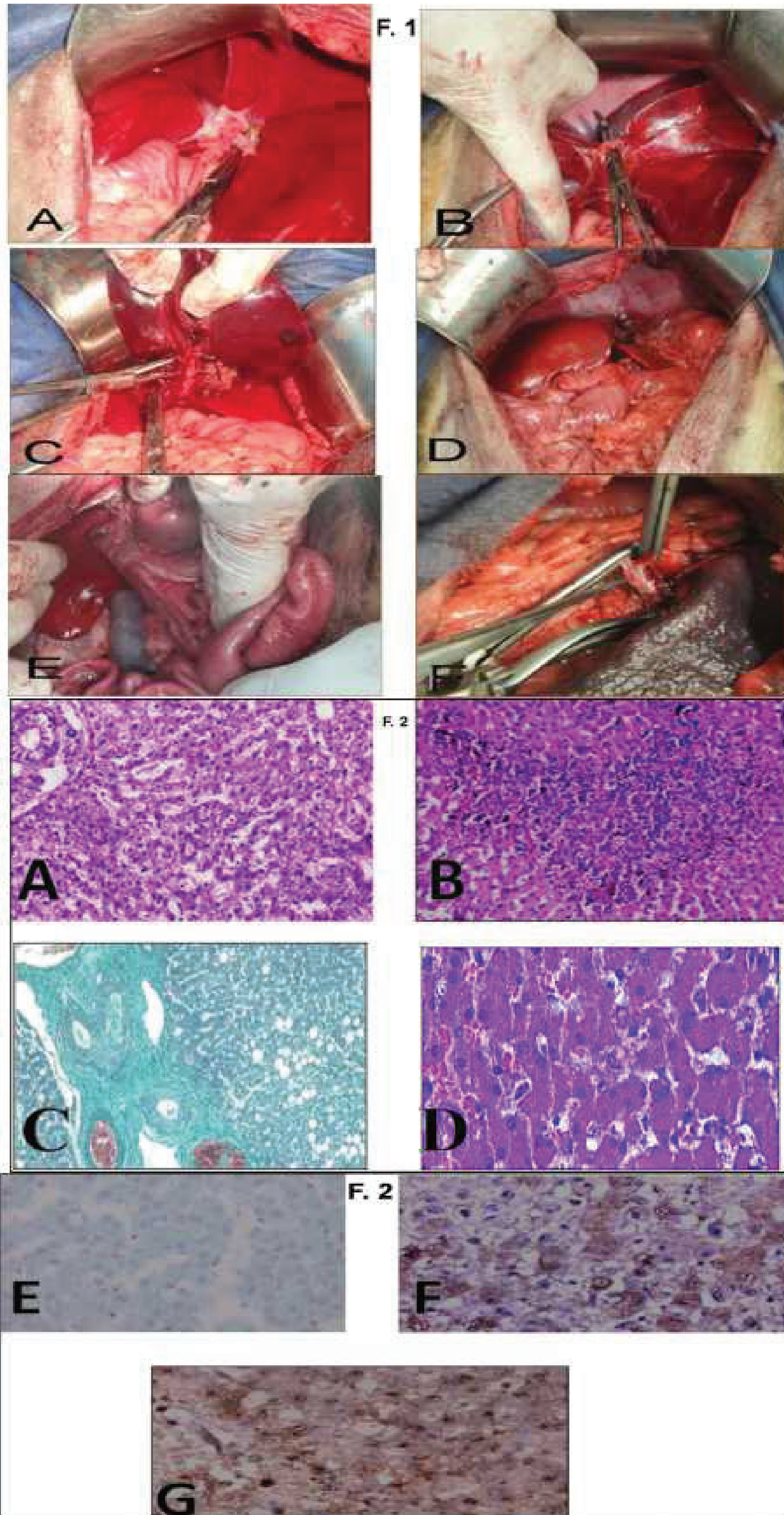
Explanation of figures

Fig.1: Intraoperative photographs of procedure of arterialization of portal vein. A: left lateral lobar portal vein and left lateral lobar hepatic vein at level of lobar fissure. B: left medial lobar portal vein: dorsal to left medial biliary duct & artery. Note ischemic left lateral lobe. C: vessels of central division dissected before ligation. D: completed 65% hepatectomy plus cholecystectomy. E: caudate process of caudate lobe with exposed inferior vena cava and portal vein. F: a side-to-side shunts splenic artery and vein.

Fig. 2: Histopathological results of the biopsies taken from Groups. A: A case from G1, showed peri portal hepatic ballooning and hydropic degeneration involved 50% of hepatocytes (H&E ×200). B: Biopsy from G2 showed more marked necrosis,fragmentation and dense inflammatory infiltrate (H&E ×200). C: Biopsy from G3 showed expanded portal tracts by fibrosis, proliferated, dilated and congested portal blood vessels (Masson trichome×40). D: G3: biopsy showed thickened cord plates, hypertrophy and hyperplasia of Kupffer cells (H&E ×40). E: G3 showed binucleated hepatocytes in 15% of hepatocytes (Masson trichome x 40). F: G1, showing proliferating hepatocytes expressing P105 40% of hepatocytes (Immunostain ×400). G: 75% of hepatocytes strongly expressing P105, a biopsy from G3 (Immunostain ×400).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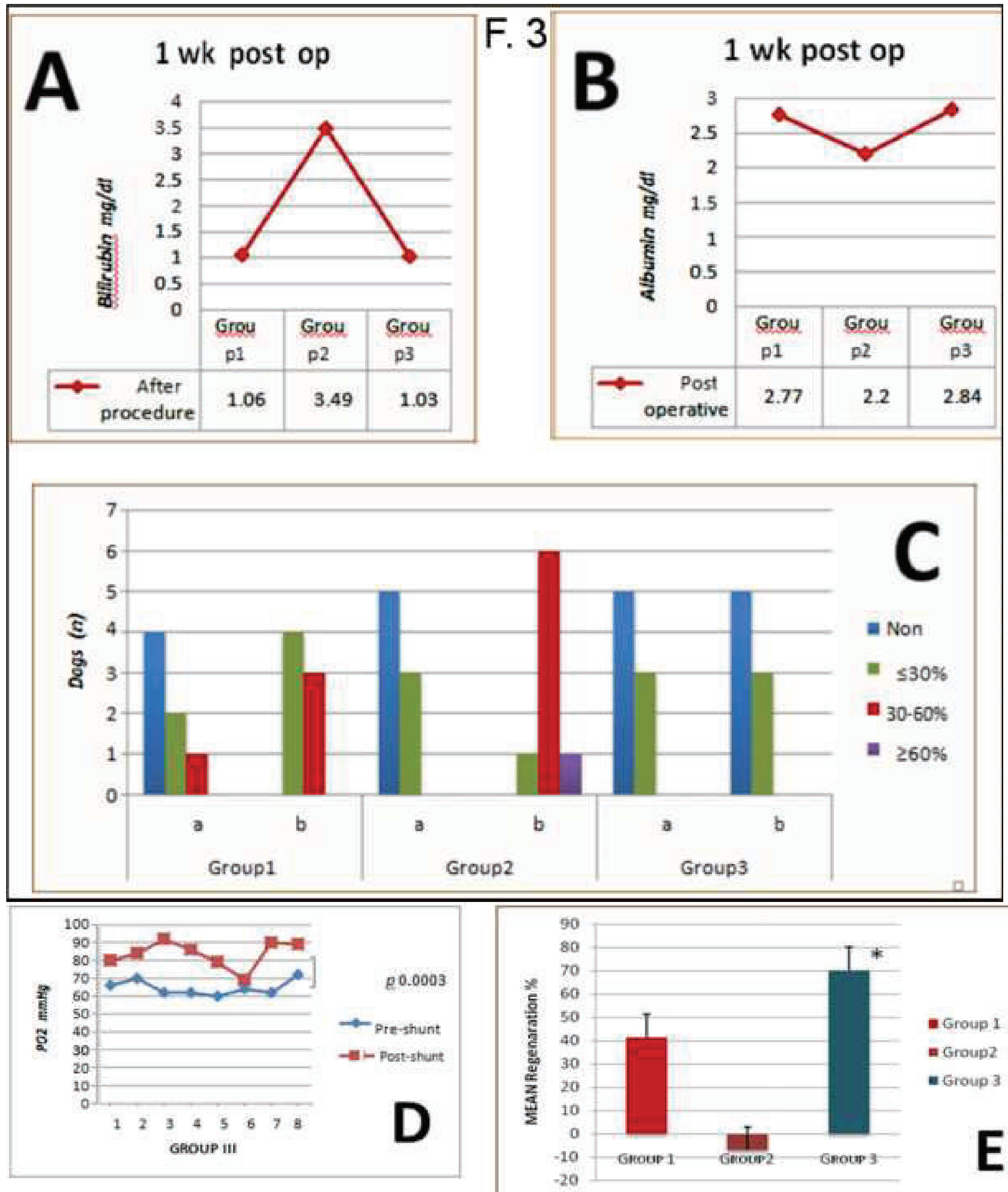

Fig.3**: A:** Post-operative Bilirubin levels mg/dl. **B**: Post-operative Albumin levels mg/dl. **C**: Degenerative indicator between three groups (hydropic degeneration/ballooning) a=pre-operative b=post-operative. **D**: PO2 levels pre and post shunt. **E**: Chart showing the mean regeneration % between the 3 groups *= p (0.007)

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