

LETTERS TO THE EDITOR

CHOLESTASIS IN A MURINE EXPERIMENTAL MODEL: LESIONS INCLUDE HEPATOCYTE ISCHEMIC NECROSIS

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We have read the paper of Prado et al. with great interest. The main purpose of the study was to establish a murine experimental model of cholestasis, in order to study, in future investigations, the effects of drugs that could delay or prevent the development of cirrhosis in patients with biliary obstruction. The paper is very interesting and deserves some important considerations:

1. The authors describe that “the common bile duct was isolated, doubly ligated and resected between the ligatures” and they conclude that this surgical procedure provoked “dilatation and proliferation of bile ducts with frequent areas of ischemic necrosis”. Emphasis is given to the hepatocyte ischemic necrosis as a consequence of the common bile duct ligation. Since we have been working with a similar model in newborn rats (weight 8-14grams) in our laboratory (Pediatric Surgery Laboratory – LIM-30 FMUSP) we have experience to conclude that the authors accidentally ligated the hepatic artery. This artery is too thin and situated very close to the common bile duct, and cannot be identified without the utilization of magnification loupes, as we verified in the initial phase of our experience (pilot plan). Besides that, the high index rate (82%) of mortality in the early postoperative period is clear evidence that the artery was accidentally ligated and mainly because the hepatic hilus was extensively manipulated, similar to our initial conclusions. Finally, we verified that the isolated common bile duct ligation provokes peripheral ductal proliferation in the portal space without any hepatocyte necrosis and with high index of animal survival.

2. I suggest the authors to repeat the experiment and perform the surgical procedure with 3.5X magnification loupe and ligate the common bile duct with two delicate 8-0 mononylon stitches without resecting any segment of bile duct, as we do in our newborn rat model.

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We thank Dr. Uenis Tannuri's attention concerning our results. We must emphasize some important details that unfortunately have not been mentioned.

We are sure that we have not sectioned the hepatic artery, since:

- 1) in all surgical procedures we routinely used magnification loupes;
- 2) by the time our first results demonstrated areas of necrosis resembling hepatic ischemia, we strongly considered the hypothesis of blood vessel lesion. The experiments were repeated, always using magnification loupes, with identification of hepatic artery during the experiments;
- 3) we have worked with adult and heavier animals than the ones by Dr Tannuri (14-28 g versus 8-14 g), which might have facilitated hepatic artery visualization;
- 4) additionally, in order not to extensively manipulate hepatic hilus, the common bile duct ligation was always done at its distal part, as far as possible from the hepatic hilus;
- 5) even if lesion or hepatic artery still had occurred, one should expect areas of necrosis to be larger than the ones observed and to follow a segmental pattern. In our study, we have found scattered small areas of ischemic necrosis within areas of preserved hepatic tissue;
- 6) And finally, one must consider an additional probable mechanism for these achievements: a secondary ischemic necrosis due to a vascular thrombosis related to the inflammation taking place around the cholangiolytic infection process.

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