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УЧРЕЖДЕНИЕ

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Animal care and use statement

The animal protocol was designed to minimize pain or discomfort to the animals. The animals were operated under general anesthesia with diethyl ether (Medhimprom, Moscow region, Russia; 0.08 ml per liter of chamber volume), between 9 am and 11 am. Diethyl ether is commonly used as an anesthetic in modeling liver regeneration via hepatectomy. In our setting, it provided the least negative effect on animal survival as compared with its alternatives, Zoletil ®100 and isoflurane, probably due to its high pulmonary clearance rates (estimated 90% of the absorbed diethyl ether is exhaled unchanged) in combination with the minimal contribution of hepatic metabolism to the rates of its excretion.

The surgery was performed between 09:00 am and 11:00 pm to minimize potential variability in the progression of liver regeneration associated with surgery time and the circadian clock. The borderline condition produced by subtotal 80% hepatectomy in a rat is described as an acute liver failure; it is externally manifested as reduced overall mobility of the animal combined with piloerection. The condition is resolved in the course of 48 h by either spontaneous death of the

animal or switch to the rapid recovery, and no means for apriori distinction between the survivors and non-survivors have been reported. In connection with this layout, the animal health was inspected 4 times a day during the first 48 h after the surgery, and subsequently 2 times a day until the sacrifice.

The operated animals, two per cage, were housed for recovery in a temperature-regulated room with a 12:12 h light-dark cycle and unlimited access to food and water. Meloxicam (1.0 mg/kg/day) was repeatedly injected into the neck fat pad as postoperative analgesia for two days after the surgery; additionally, gentamicin (3.0 mg/kg/day) was injected subcutaneously as an antibiotic on the first day after the surgery.

The animals were drawn from the experiment in CO<sub>2</sub>-chamber at 3 h, 6 h, 24 h, 48 h, 72 h, 7 days, or 10 days after the surgery.

All experimental work involving animals was carried out according to the standards of laboratory practice (National Guidelines No. 267 by Ministry of Healthcare of the Russian Federation, June 1, 2003), and all efforts were made to minimize suffering.

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