**Name of Journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 31762**

**Manuscript Type: ORIGINAL ARTICLE**

***Basic Study***

**A****rtificial****liver** **support in pigs with acetaminophen-induced acute liver failure**

He GL *et al*.Artificial liver system treated APAP-induced porcine model.

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**Author contributions:** Pan MX and Gao Y designed research; He GL, Jiang ZS, Cheng Y, Zhou CJ and Gao Y performed research; He gl, Zhou cj and Cheng y analyzed data; He gl wrote the paper.

**Institutional review board statement:** The study was reviewed and approved by the Zhujiang Hospital Institutional Review Board.

**Institutional animal care and use committee statement:** All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Guangdong province [IACUC protocol number: SCXK (Guangdong) 2011-0015].

**Conflict-of-interest statement:** No conflict of interest exists.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Unsolicited manuscript

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**Received:** December 6, 2016

**Peer-review started:** December 6, 2016

**First decision:** December 29, 2016

**Revised:** January 24, 2017

**Accepted:** March 20, 2017

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To establish a reversible porcine model of acute liver failure and treat it with an artificial liver system.

***METHODS***

Sixteen pigs weighing approximately 30–35 kg were chosen and administrated acetaminophen (APAP), then randomly assigned to two groups; eleven were in the experimental group, in which a treatment procedure was performed, whereas the rest (*n* = 5) were included in the control group. Treatment was started after dosing acetaminophen for 20 h and continued for 8 h. Clinical manifestations of all animals, including liver and kidney functions, serum biochemical parameters and survival times were analyzed.

***RESULTS***

Twenty hours after dosing with APAP, the levels of serum aspartate aminotransferase, total bilirubin, creatinine and ammonia were significantly increased; meanwhile, albumin levels were decreased (*P* < 0.05). Prothrombin time was found to be extended with progression of acute liver failure (ALF). After continuous treatment for 8 h (at 28 h), aspartate aminotransferase, total bilirubin, creatinine, and ammonia showed a decrease in comparison with the control group (*P* < 0.05). A cross-section of livers revealed signs of vacuolar degeneration, nuclear fragmentation and dissolution. Concerning survival, porcine models in the treatment group survived for longer times with artificial liver system treatment (*P* < 0.05).

***CONCLUSION***

This model is reproducible and allow for the mensurable evaluation of new liver systems, such as a bioartificial liver. The artificial liver system(ZHJ-3) is safe and effective for acetaminophen-induced porcine ALF model.

**Key words:** Hepatic failure; Acetaminophen; Artificial liver; Acute liver failure; Liver-assisted device

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**Core tip:** This is an article about an artificial liver system that was used to treat an acetaminophen (APAP)-induced porcine acute liver failure (ALF) model. An APAP porcine ALF model was set up and treated by an artificial liver system. The artificial liver system(ZHJ-3) improved serum biochemistry levels and extended porcine survival times significantly. This study concluded that the APAP-induced model is reproducible and and allow for the mensurable evaluation of new liver systems, such as a bioartificial liver, for the support of hepatic failure in humans. The artificial liver system(ZHJ-3) is safe and effective for APAP-induced porcine ALF model.

He GL, Feng L, Cai L, Zhou CJ, Cheng Y, Jiang ZS, Pan MX, Gao Y. Artificial liver support in pigs with acetaminophen-induced acute liver failure. *World J Gastroenterol* 2017; In press

**Introduction**

Acute liver failure (ALF) is defined as sudden and severe liver dysfunction with rapid development of coagulopathy, encephalopathy, and multi-organ failure[1,2]. The mortality due to liver failure remains exceedingly high, and liver transplantation is still the only effective treatment to improve survival[3,4]. However, liver transplantation is hampered by the severe shortage of donor organs[5]. A large animal model of ALF, which simulates the human clinical syndrome, has a predictable time course to death but also has the potential for reversal of liver failure[6].

Animal models simulating ALF are not only needed to study the underlying poorly understood pathophysiological mechanisms but are also important for the evaluation of new liver support systems prior to introduction in clinical studies. A devascularization surgical model of ALF is one of the most common animal models used for evaluating liver support systems[7]. Terblanche and Hickman[8] suggested certain criteria that an ideal model should satisfy: (1) the induced hepatic failure should be potentially reversible; (2) liver damage should be reproducible; (3) selective liver damage should occur that leads to death from liver failure during an interval similar to that seen clinically; (4) death should occur sufficiently long enough from the insult to provide a suitable therapeutic window; (5) a large animal should be used to make possible the use of therapies applicable to humans; and (6) the toxin should present minimal risks to laboratory personnel.

Acetaminophen (APAP) is one of the most widely used analgesics, with few side effects when taken in therapeutic doses[9]. An overdose of acetaminophen, taken either accidentally or deliberately, induces hepatotoxicity leading to severe hepatic damage, which may cause ALF[10]. Currently, acetaminophen overdose is the number one cause of ALF in the United States and Europe[11,12]. Newsome and his coworkers[13] completed steady blood concentrations of APAP without fatal methemoglobinemia. Thiel *et al*[14] used jejunal administration of APAP, and Lee *et al*[15] made a successful APAP-induced ALF porcine model.

This paper studies a APAP-induced porcine models of ALF, which aims to improve efficiency and result. In this study we evaluates the safety and efficacy of a liver support system (ZHJ-3), a type of bioartificial liver system which incorporates many functions. We use the artificial liver part to support ALF model. The aims for the work were (1) to establish a stable and efficient APAP-induced ALF porcine model; and (2) to evaluate the safety and efficacy of ZHJ-3.

**MATERIALS AND METHODS**

***Animals and reagents***

Sixteen 6–7 month old healthy Tibet mini pigs (weight 30–35 kg) obtained from the animal center of Southern Medical University (Certificate of Conformity SCXK (Guangdong) 2011-0015 complying with the GB 14925-94 proposal for all experimental pigs) were used in this study. All the animals received humane care and the study protocols were in compliance with the animal care guidelines established by Southern Medical University. The project was approved by the institutional review board of the second affiliated hospital of Southern Medical University, Guangzhou, China (No. ZJYY-2014-GDEK-003).

***Model set-up***

Experimental pigs were on preoperative fasting for 10 h and were only provided water. Xylazine hydrochloride injection (0.15-0.2 ml/kg) was used as an intramuscular injection for anesthesia. Using paraffin oil as a lubricant, a stomach tube was fixed in front with the left hand holding the gauze holding stomach tube, and the right hand holding forceps clipping the stomach tube along the mouth, thus inserting the gastric tube to the scheduled length. The preliminary stomach tube was fixed and checked to determine whether the tube was in front of the mouth. Then, the gastric juice was extracted after the tube was located in the stomach, and tape used to fix the tube on the cheek. Pigs were thus maintained under general anesthesia, which was induced with xylazine hydrochloride (0.5–1.0 ml/kg), and maintained intravenously with propofol (0.2 ml/kg per hour). Omeprazole (40 mg) was given through intravenous to prevent gastric ulceration, and cefoperazone (20 mg/kg intravenous) was given as a preventive antibiotic through the peri-operative to prevent infection. A 5Fr catheter (Guangdong Baihe Medical Technology Co, Ltd) was inserted into the jugular vein for fluid and drug administration and for measuring hemodynamic parameters. A double lumen catheter (12Fr) (Guangdong Baihe Medical Technology Co, Ltd, Guangzhou, China) was placed into the femoral vein for artificial liver treatment.

***Establishment of the ALF model***

Acute liver failure was induced with APAP tablets, which were dissolved in 50 ml of normal saline and administered via the oro-duodenal feeding tube. A loading dose of 0.3 g/kg APAP was given at time zero, followed by a maintenance dose per hour until the 12 h. The maintenance APAP dose was 3.0 g, which aimed to keep arterial methemoglobin (metHb) concentrations at 1%–5% of the total hemoglobin. All the pigs were divided into two groups randomly, eleven in treatment group and five used as control group.

***Supportive care***

Fluid replacement solutions were given at 5 ml/kg per hour *via* the jugular vein throughout the whole research period: Sodium Lactate Ringer's Injection , 0.9% sodium chloride and 5% glucose was given at the beginning of this research for the electrolyte and acid–base balance, glucose level. Colloid solution voluven (hydroxyethyl starch 130/0.4 Sodium Chloride Injection) was given intravenously starting at 1 ml/kg per hour. 25% human albumin was given intravenously when albumin levels dropped to less than 10 g/l.

***Artificial liver therapy***

Artificial liver treatment was started as soon as 20 h after APAP administration and continued for 8 h. Heparin was given to treatment group animals by continuous infusion. APTT was monitored for adjusting the rate of heparin pump. The blood pump flow was adjusted to 50 mL/min, ultrafiltration rate was setted to 20%. 200 ml 0.9% saline was injected into the tube every 2 h to prevent the filter and tubing from clogging.

***End of study in treatment and controls***

The study end point was death for the control group animals. For treatment group, animals were sacrificed with intravenous pentobarbital 5 d after induction of ALF.

***Biochemical index assessment***

Blood samples were gathered before the administration of APAP (0 h) and at fixed intervals (every 2 h after administration of APAP) to observe aspartate transaminase (AST), albumin (Alb), total bilirubin (Tbil), ammonia (NH3), creatinine (Cr), and prothrombin time (PT) until the animals died.

***Histological examination***

Tissue specimens were fixed in 4% paraformaldehyde solution 24 h to 36 h, decalcified by 10% EDTA, sliced and paraffin embedded, which was followed by step-by-step alcohol dehydration. Then, the changes were observed with HE staining under a light microscope. For electron microscopy, good liver tissue was immediately placed in a 0.1-mol/l dimethyl mixture of sodium arsenate buffer in 2.5% glutaraldehyde and fixed at 4 ℃ for 2 h. Then, 0.1 mol/l sodium dimethyl arsenic acid buffer was used for washing three times in the same buffer made up with 1% osmic acid, and the tissue was fixed for 2 h.

***Animal care and use statement***

The animals which lived in the end of the experiment were euthanized by barbiturate overdose for tissue collection.

***Statistical analysis***

The mean ± SD of the analyzed parameters obtained before, during, and after the administration of APAP were compared with a *t* test. A *P* value <0.05 was considered significant.

**RESULTS**

***Vital signs of pigs***

No Tibet mini pigs with ALF died during the treatment. There was no divulgation in the piping of ZHJ-3 and no significant hemorrhage, allergies, or other adverse reactions found in the pigs during the whole treatment. The HR(heart rate), SPO2(oxyhemoglobin saturation), respiration rate, and artery blood pressure keeped stable in the treatment (Table 1).

***Serum biochemical parameters***

We observed a rapid reduction in animal food intake from 12 hours after APAP administration, and as shown in Table 2 and Figure 1, the serum AST level increased with progression of ALF. The levels of NH3, Tbil, and Cr were significantly increased after APAP administration in comparison with their levels before administration of APAP (*P* < 0.05). However, serum albumin levels after APAP administration were significantly decreased (*P*<0.05). PT was found to be increased with increasing times of APAP administration. The treatment for 8 h after APAP administration (*i.e.*, 28 h) caused a significant decrease in AST, Tbil, NH3 and Cr levels than the control group animals (*P* < 0.05, Figure 1). This indicated that the APAP-induced porcine models of ALF was established successfully.

***Histological observation***

In the ALF control group, The livers were slightly enlarged, soft, blunt in the edges, and showed smooth liver capsules, mottled surface and seattered from Pin-Point like to rice-like bleeding Points. There was kermesinus congestion on the cut surface of liver with yellow chyliform necrotic tissues. Cross sections of the livers showed blood congestion,the rest of the livers were red or brownish gray in color. Hepatocytes showed diffuse swelling and were sinusoidal. After given APAP, the hepatic ultrastructure were observed with an electron microscope：homogenized glycogenosome in cytoplasma, endoplasma, reticulum degranulation, swelling mitochondria with obscure mitochondrial crista,some dissolved mitochondria, abnormal nucleus with congested chromatin and intranuclear pseudoinclusions and significant decrease of intracellular bile canaliculi. (Figure 2).

***Survival analysis***

In the treatment group, five of the eleven porcine models survived with an average duration of survival of 84 h, while five died in the control group， which average survival time is 61 h. The artificial liver support system (ZHJ-3) prolonged the survival time significantly.(*P* < 0.05, Figure 3). Of the five survival porcine models,one died at 123 h, the other four porcine models survived for more than 5 d and were sacrificed.

**Discussion**

The artificial liver support systems devised to provide a transitional treatment for ALF patients awaiting compatible organs. For the pre-clinical evaluation of artificial liver support systems, a stable and reproducible large animal ALF model was proposed[16-18].

Acetaminophen is generally considered a safe drug for pain relief or fever reduction, but the incidence rate of toxicity leading to ALF has been steadily increasing[19]. Previous attempts to establish a standardized acetaminophen intoxication model[13-15,20] were unsuccessful. Thiel *et al*[20] administered acetaminophen directly into the upper jejunum via an implanted catheter, and this route of administration was affected by anesthesia, laparotomy and jejunotomy. Lee *et al*[15] used an oro-duodenal feeding tube that was placed for APAP dosing without any surgery. The way a gastric tube is used for paracetamol injection not only avoids a complex operation but also facilitates basic anesthesia intubation, thus greatly facilitating the induction of hepatic failure. Therefore, we used an oro-duodenal tube to administer acetaminophen. Splanchnic blood flow and the volume, composition and pH of alimentary secretions are known to alter the rate of acetaminophen absorption in experimental animals[21] but do not influence the controllability of acetaminophen intoxication. This, along with the intensive support provided, produced a reproducible clinically relevant model of ALF. However, the current model might be criticized for testing acetaminophen intoxication in a less clinically applicable situation because animals underwent general anesthesia and pretreatment with antibiotics[22].

The treatment with this artificial liver system improved survival by supporting the detoxification function of the liver and the kidney, thereby interrupting the vicious cycles of elevated toxin levels and the resultant worsening of multiple organ failure. The artificial liver system improved the levels of liver biochemical index, such as AST and Tbil in the ALF animal, but treatment resulted in significant decreases in albumin levels, resulting likely from lack of bioreactor hepatocytes[23-25]. In cirrhotic patients, albumin has been shown to be a highly effective plasma expander[26,27]. Albumin infusion began when albumin levels dropped to less than 10 g/l to avoid marked hemodynamic instability. The albumin dosing regimen was based on Tympa *et al*[28] pilot studies in this research.

Artwohl *et al*[29] and Henne-Bruns *et al*[30] realized that acetaminophen-dependent toxic side effects produced major complications in their studies. Acetaminophen plasma level-adapted intoxication was used to minimize complications. Significant methemoglobinemia was prevented by adjusting APAP dosing to a percentage of methemoglobin; once methemoglobin exceeded 1%, serum APAP concentrations were > 300 mg/l, and the APAP dose could be reduced. Thiel *et al* noted that a toxic plasma acetaminophen range between 300 mg/l and 450 mg/l produced a reproducible large animal model of ALF.

Therefore, the APAP-induced porcine model of ALF is a reproducible way to test the artificial liver system, and this system(ZHJ-3) can improve the porcine biochemical levels and extend the survival time.

The major limitation of this study was the small number of animals with ALF, which may lead to incorrect conclusions. In addition, the meta-analyses may be affected by bias. However, the studies included in this analysis were homogenous, and the sensitivity analysis revealed stability of the conclusions.

**ACKNOWLEDGEMENTS**

We appreciative of those authors of the original research. And we thank American Journal Experts for the modification .

**comments**

***Background***

Acute liver failure (ALF) is the sudden loss of hepatic function, The mortality remains exceedingly high. The study was aim to establish a simple and reversible pig model of acetaminophen-induced ALF,and to evaluate the effectiveness and safety of artificial liver system (ZHJ-3). The study concluded that the acetaminophen (APAP)-induced model is reproducible and should allow quantitative evaluation of new technologies, such as a bioartificial liver, for the support of hepatic failure in humans.

***Research frontiers***

It is a lot of studies about the acute liver failure.But there has been few previous reported study of the APAP-induced porcine model in acute liver failure.

***Innovations and breakthroughs***

In this study, using stomach tube administrateAPAP is simple and reproducible way to set up a porcine ALF model. The artificial liver significantly reduced serum biochemistry levels and extended animal survival times.

***Applications***

The study concluded that the APAP-induced model is reproducible and should allow quantitative evaluation of new technologies, such as a bioartificial liver, for the support of hepatic failure in humans.

***Peer-review***

This is a very interesting paper about the treatment of APAP-induced porcine model using artificial liver system. The most important innovations of this study is APAP administration procedure, by using stomach tube.It is a simple and reproducible way to set up a porcine ALF model. In addition, it demonstated that the artificial liver system (ZHJ-3) significantly reduced serum biochemistry levels and extended animal survival times..

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**P-Reviewer:** Berg T, Tsoulfas G **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 values of vital signs of pig at each time point (mean±SD)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time(h)** | **Heart rate** **(per min)** | **Respiratory rate (per min)** | **SPO2****(%)** | **Artery blood pressure****( mmHg)** |
| 0 | 84±4 |  25±13 | 96±2 | 103±4 |
| 1 | 79±4 | 21±3 | 91±7 | 100±5 |
| 2 | 74±4 | 23±5 | 94±5 | 101±9 |
| 3 | 80±5 | 21±3 | 96±2 |  99±6 |
| 4 | 89±8 | 24±6 | 93±7 |  96±11 |
| 5 | 91±7 | 21±4 | 92±3 |  91±7 |
| 6 | 79±4 | 19±3 | 94±5 |  98±5 |
| 7 | 76±7 | 20±3 | 95±2 | 100±2 |
| 8 | 83±5 | 23±6 | 92±5 |  97±6 |

**Table 2 Serum biochemistry with Acetaminophen administration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Indicators** | **before** **administration****treatment control** | **20 h after** **administration****treatment control** | **28 h after** **administration****treatment control** |  |
| AST (U/L) | 37.8±5.5 | 44.8±6.5 | 460.6±22.9a | 410.2±13.5a | 108.8±13.2c | 522.1±29.5 |
|  NH3 (g/dl) | 26.9±4.1 | 37.4±5.6 | 134.1±11.1a | 149.1±8.3a | 96.7±16.9c | 170.3±23.9 |
| TBiL (μmol/L) | 22.4±1.9 | 24.5±1.1 | 97.8±15.3a | 105.5±6.1a | 66.7±12.4c | 170.2±37.8 |
| Cr (μmol/L) | 56.1±4.4 | 55.9±7.6 | 175.7±19.5a | 166±10.3a | 119.4±10.4c | 263.1±9.1 |
| ALB (g/L) | 35.9±2.1 | 31.7±0.9 | 22.2±3.2a | 20.4±2.8a | 21.4±1.3 | 19±1 |
| PT(s) | 11.6±3.2 | 13±3.0 | 60.8±9.3a | 70.2±4.9a | 73.0±7.7 | 85.8±9.2 |

a*P* < 0.05, 20 h after administration *vs* before administration; c*P* < 0.05, 28 h after administration treatment *vs* control.



**Figure 1 Survival curve of the porcine models in the treatment and control groups.**



**Figure 2 Hepatocytes swelling, nuclear fragmentation, and dissolution.()** electron microscopy ×10800.



**Figure 3 Changes in the serum biochemical parameters before (baseline) and 20 h after administration of** acetaminophen**.** Serum AST, Tbil, NH3, and Cr levels were increased, while alb levels showed a decrease. Prothrombin time was prolonged. About 28 h after administration of acetaminophen, AST, Tbil, NH3 and Cr remains elevated while alb remains decreased. But in the bioartificial liver system groups, AST, Tbil, NH3 and Cr decreased significantly in comparison with control group. a*P* < 0.05 *vs* control group.