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BRIEF ARTICLE

High incidence of biliary complications in rat liver transplantation: Can we avoid it?

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Abstract

AIM: To investigate how to reduce the incidence of biliary complications in rat orthotopic liver transplantation.

METHODS: A total of 165 male Wistar rats were randomly divided into three groups: Group A, orthotropic liver transplantation with modified "two-cuff" technique; Group B, bile duct was cut and reconstructed without transplantation; and Group C, only laparotomy was performed. Based on the approaches used for biliary reconstruction, Group A was divided into two sub-groups: A1 (n = 30), duct-duct reconstruction, and A2 (n = 30), duct-duodenum reconstruction. To study the influence of artery reconstruction on bile duct complication, Group B was divided into four sub-groups: B1 (n = 10), duct-duct reconstruction with hepatic artery ligation, B2 (n = 10), duct-duct reconstruction without hepatic artery ligation, B3 (n = 10), duct-duodenum reconstruction with hepatic artery ligation, and B4 (n = 10), duct-duodenum reconstruction without hepatic artery ligation. The samples were harvested 14 d after operation or at the time when significant biliary complication was found.

RESULTS: In Group A, the anhepatic phase was 13.7 ± 1.06 min, and cold ischemia time was 50.5 ± 8.6 min. There was no significant difference between A1 and A2 in the operation duration. The time for biliary reconstruction was almost the same among all groups. The success rate for transplantation was 98.3% (59/60). Significant differences were found in the incidence of biliary complications in Groups A (41.7%), B (27.5%) and C (0%). A2 was more likely to have biliary complications than A1 (50% *vs* 33.3%). B3 had the highest incidence of biliary complications in Group B.

CONCLUSION: Biliary complications are almost inevitable using the classical "two cuff" techniques, and duct-duodenum reconstruction is not an ideal option in rat orthotopic liver transplantation.

Key words: Rat; Liver transplantation; Biliary complication; Animal model

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INTRODUCTION

The occurrence of biliary complications (BC) remains one of the most critical challenges in clinical liver transplantation. According to the literature, the incidence of biliary complication for living-donor liver transplantations (LDLT) is as high as 64%[1-9]. Biliary complications have made biliary reconstruction the "Achilles heel" of liver transplantation. In rat liver transplantation, the occurrence of biliary complications has become a confounding factor in the judgment of experimental results and an obstacle to the practice of transplantion. Unfortunately, few researches could be found to report the incidence of biliary complications in rat liver transplantation. In this study, we investigated the biliary complications after rat orthotopic liver transplantation (ROLT), trying to find a better approach to biliary reconstruction and reduce the incidence of biliary complications after transplantation.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 200-250 g, were purchased from the Experimental Animal Center of Sun-Yat Sen University and fed in the specific pathogen free (SPF) animal lab. The weight of the recipient was similar to that of the donor. All animals had free access to food and water except the recipients, which had been fasted for 12 h before operation.

Technique

ROLTs were performed using the "two-cuff" technique established by Kamada[10,11]. All surgical procedures were performed by a single operator under naked eye. Napental was used for the anesthesia (40 mg/kg). All experiments were performed in compliance with the standards for animal use and care set by institutional animal care and use Committee.

Donor operation

After laparotomy, the left subphrenic vein was ligated and all the perihepatic ligaments were divided. The bile duct was incised and a stent (0.9-mm inner diameter, 4-mm length) was introduced and tied firmly. The right renal vein was dissociated and the right adrenal venous plexus was ligated. After 150 units of heparin was injected to form systemic heparinization, the liver was irrigated with physiological saline containing heparin (20 U/mL) through the aorta distal to the celiac artery. At the same time, infrahepatic inferior vena cava (IHIVC) and suprahepatic inferior vena cava (SHIVC) were dissected to allow outflow of the perfusate. When the liver turned khaki color, SHIVC was divided along the diaphragm (without the phrenic ring) , and the right renal vein, the portal vein (PV) and IHIVC were skeletonized and divided. The liver was then harvested and the graft was preserved at 4℃ in physiological saline with 20 U/mL heparin.

The PV was induced through the cuff (2-mm inner diameter, 3.5-mm length) and the distal end of the vein was completely reversed and fixed onto the cuff with a 5-0 silk ligation. The same method was used to prepare the cuff (3-mm inner diameter, 4-mm length) for IHIVC. The SHIVC was treated with two 8-0 silk sutures pierced via the two corners of the vein.

Recipient operation

After laparotomy, the self-made retractor was used to expose the operative area, and the left subphrenic vein. The transport vessels between the left liver and esophagus, hepatic artery and the right adrenal venous plexus were ligated orderly. One necessary step was to put a rubber under the SHIVC for the purpose of traction when removing the liver. Then IHIVC and PV were clamped to the anhepatic phase. SHIVC was blocked after exsanguination and the liver removed quickly. SHIVC was sutured by an end to end anastomosis (8-0, nylon suture), PV was reconstructed by means of cuff technique and the anhepatic phase was ended. The same method was used to reconstruct IHIVC. Based on the experimental design, the bile duct was reconstructed differently.

The recipient rats were fasted for at least 12 h after operation but water was permitted.

Biliary reconstruction and hepatic artery ligation

There were two ways to rebuild the biliary tract in this experiment: (1) end-to-end anastomosis with the stent; and (2) end-to-side anastomosis between bile duct and duodenum (1-2 cm away from the pylorus) with the stent.

Experimental design

One hundred and sixty-five male Wistar rats were randomly divided into three groups: Group A, orthotropic liver transplantation by modified two-cuff method; Group B, bile duct was cut and reconstructed without orthotopic liver transplantation; and Group C, sham-operation group. Based on the approaches of biliary reconstruction, Group A was divided into two sub-groups: A1 (n = 30), duct-duct reconstruction, and A2 (n = 30), duct-duodenum reconstruction. To study the influence of hepatic artery on bile duct complication, Group B was divided into four subgroups: B1 (n = 10), duct-duct reconstruction with hepatic artery ligation; B2 (n = 10), duct-duct reconstruction without hepatic artery ligation; B3 (n = 10), duct-duodenum reconstruction with hepatic artery ligation, and B4 (n = 10), duct-duodenum reconstruction without hepatic artery ligation. In Group C (n = 5), only laparotomy was performed.

Samples were harvested 14 d after operation or at the time when any significant biliary complication was found. Serologic samples were collected to test the levels of aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL), gummaglutamyl transpeptidase (GGT) and alkaline phosphatase (ALP). Biliary complications were determined by pathologic examination and serologic analysis.

Statistical analysis

Data were expressed as mean ± SD. Statistical differences

Table 1 Incidence rates of biliary complications in different groups

Groups	*n*	Abscess	Sludge	EBD	IBD	Total	
Group A							41.7%[e] (25/60)
A1	30	26.70% (8/30)	13.30% (4/30)	26.70% (8/30)	13.30% (4/30)	33.30% (10/30)	
A2	30	43.30% (13/30)	20% (6/30)	26.70% (8/30)	10% (3/30)	50%[a] (15/30)	
Group B							32.50% (13/40)
B1	10	10% (1/10)	0	30% (3/10)	0	30% (3/10)	
B2	10	10% (1/10)	0	20% (2/10)	10% (1/10)	20% (2/10)	
B3	10	30% (3/10)	20% (2/10)	40% (4/10)	10% (1/10)	50%[c] (5/10)	
B4	10	20% (2/10)	10% (1/10)	30% (3/10)	10%*t* (1/10)	30% (3/10)	
Group C	5	0	0	0	0	0	0
Total	105	26.70% (28/105)	12.40% (13/105)	26.70% (28/105)	9.52% (10/105)	36.20% (38/105)	

Some rats had two (or more) kinds of biliary complications at the same time. [a]$P < 0.05$ *vs* A1; [c]$P < 0.05$ *vs* B1, B2 and B4; [e]$P < 0.05$ *vs* groups B and C EBD: Extrahepatic biliary dilatation; IBD: Intrahepatic biliary dilatation.

between the control and the experimental groups were analyzed using analysis of variance. $P < 0.05$ was considered statistically significant.

RESULTS

Operation time and success rate

In transplantation groups, the anhepatic phase was 13.7 ± 1.06 min, and cold ischemia time was 50.5 ± 8.6 min. There was no significant difference between A1 and A2 in operating time ($P > 0.05$). And the time for biliary reconstruction was almost the same among all groups ($P > 0.05$).

Recipients surviving at least 24 h were considered as success. The success rate of ROLT was 98.3% (59/60). Only one case in A1 died from bleeding at SHIVC 8 h after operation.

Biliary complications

The incidence rate of biliary complications was 41.7% in Group A, which was much higher than that in Group B (32.5%) and Group C (0%), with significant differences among the three groups ($P < 0.05$). After transplantation, A2 had a higher incidence of biliary complications than A1 (50% *vs* 33.3%, $P < 0.05$). B3 had the highest incidence of biliary complications among the groups without orthotopic liver transplantation ($P < 0.05$). No biliary complication was found in the sham-operation group.

General observation

The color of urine turned yellow in the rats with biliary complications. Other complications were dried hair, reaction retardation, reduced appetite and activities, and eye bleeding in some rats.

Gross anatomy

Biliary complications consisted of abscess, intrahepatic and extrahepatic biliary dilatation and biliary sludge. Abscess (35%) was most frequently seen in Group A, compared with dilatation of extrahepatic bile duct (25%) in Group B. B3 had the highest incidence of biliary complications in non-transplantation groups (50% *vs* 30%, 20% and 30%) and extrahepatic biliary dilatation and abscess were two of the most important complications in this group (Table 1).

Histopathology

In the samples with biliary complications, infiltration of a large number of mononuclear cells in the portal area was the most common change, followed by dilatation of bile ducts. Cellular infiltration of biliary wall and degeneration of epithelial cells, dilatation of the central vein could also be seen. Some samples even showed vacuolar degeneration, necrosis and fibrous tissue hyperplasia. In samples with severe biliary dilatation, the normal bile duct structure had completely disappeared, with a large number of infiltrated inflammatory cells.

Serology

The serum levels of AST, ALT, TBIL, DBIL, GGT and ALP in Group A and Group B were significantly higher than in Group C, particularly AST and TBIL, with significant difference among the three groups ($P < 0.05$). Significant difference could be easily observed between duct-duodenum reconstruction groups and duct-duct reconstruction groups (A2 *vs* A1, B3 *vs* B1, and B4 *vs* B2, $P < 0.05$). Among non-transplantation groups, the serological changes, especially the bilirubin level, were more remarkable in groups with hepatic artery ligation than in those without (B1 *vs* B2 and B3 *vs* B4, $P < 0.05$) (Table 2).

DISCUSSION

Biliary complication is the second most common cause of graft dysfunction in liver transplantation with an incidence rate of as high as 64%[1-9]. Biliary complications may be related to various factors, including hepatic artery thrombosis or stenosis, technical reasons, as well as ischemia-reperfusion injury and immunological injury. High incidence of biliary complication has made biliary reconstruction the "Achilles heel" of liver transplantation.

It has been proved that hepatic artery plays an important role in blood supply of bile duct, the artery must be reconstructed when injured or cut during operation. In the early 90s, Engermann *et al*[12] showed that reconstruction of the hepatic artery can significantly reduce the incidence of biliary complications such as biliary fistula and biliary obstruction after ROLT. But with the cuff method introduced in 1973, ROLT without hepatic artery (HA) recon-

Table 2 Serological values in different groups

	n	AST (U/L)	ALT (U/L)	TBIL (μ mol/L)	DBIL (μ mol/L)	GGT (U/L)	ALP (U/L)
A1	30	452.2 ± 296.9	223.7 ± 194.7	17.1 ± 26.0	14.8 ± 24.1	10.5 ± 6.2	366.5 ± 173.0
A2	30	534.2 ± 373.3	272.8 ± 274.7	11.6 ± 21.8	10.2 ± 20.2	8.0 ± 7.3	282.8 ± 154.9
B1	10	146.6 ± 43.6	75 ± 17.7	0.79 ± 1.59	0.54 ± 1.26	4.6 ± 3.8	208.6 ± 76.4
B2	10	108.7 ± 26.4	70.0 ± 6.6	0.33 ± 0.25	0.09 ± 0.12	2.5 ± 0.97	190.2 ± 44.2
B3	10	359.3 ± 452.4	126.6 ± 131.9	15.1 ± 31.3	11.5 ± 24.1	7.3 ± 5.1	240 ± 152.0
B4	10	271.2 ± 275.2	119.3 ± 138.2	9.7 ± 27.3	7.42 ± 21.5	5.7 ± 2.8	236.3 ± 158.3
Group C	5	81.7 ± 13.2	60.7 ± 4.5	0.13 ± 0.15	0 ± 0	2.7 ± 0.58	281.7 ± 139.3

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; GGT: Gumma-glutamyl transpeptidase.

struction became globally accepted [13-18]. It is reasonable to speculate that biliary complications after liver transplantation might be more common in rats than that in human beings. Unfortunately, few studies can be found to investigate and report the incidence of biliary complications in ROLT. In our study, we simulated the biliary processes of ROLT in Group B, and found that the incidence of complications were significantly higher in groups with hepatic artery ligation than those without, which meant that hepatic artery might play an important role in the occurrence and development of biliary complications, but further investigations are needed to verify the definite mechanism.

Bile duct reconstruction by stent has been well accepted since Kamada introduced the "two-cuff" technique in ROLT[12-18]. But in view of our experience in over 600 cases of rat orthotopic liver transplantation, it seems that biliary complications after orthotopic liver transplantation are almost inevitable in the classical model. Several reasons might be contributed to this: Firstly, the wall of bile duct will become thicker as the rat grows up, constant inner diameter of the stent will definitely make the bile duct relatively narrow. Secondly, the stent would become a foreign body in bile, which will make the eddy come into being at the proximal stent and induce the sludge. So it is a great challenge to seek a new approach to modify the ROLT model. This new approach should reduce the incidence of biliary complications, and be easier to achieve.

Choledochojejunostomy has been proved to be an effective surgery to reconstruct the bile duct in clinical liver transplantation, which does not increase the incidence of biliary complications compared with the end-to-end anastomosis[19-22]. In our study, we simulated the method and designed the duct-duodenum reconstruction model. Unfortunately, this method did not show ideal results, the incidence of biliary complications was significantly higher in A2 (duct-duodenum reconstruction) than that in A2 (duct-duct reconstruction) due to the following reasons: in ROLT, the stent is directly driven into the upper part of the duodenum, which makes the stent easily obstructed by chime and then more likely to have biliary complications. Based on our study, although choledochojejunostomy has been widely used in liver transplantation, duct-duodenum reconstruction is obviously not an ideal choice in ROLT.

In conclusion, biliary complications are almost inevitable using the classical "two-cuff" technique. More attention should be paid to the occurrence of biliary complications in ROLT model. The established mode of hepatic artery and biliary reconstruction should be modified.

COMMENTS

Background

Biliary complication is the second most common cause of graft dysfunction in liver transplantation with an incidence rate of as high as 64%. Unfortunately, few researches could be found to report the incidence of biliary complications in rat liver transplantation. In this study, the authors investigated the biliary complications after rat orthotopic liver transplantation, trying to find a better way to perform biliary reconstruction and reduce the incidence of biliary complications after transplantation

Research frontiers

Classical rat liver transplantation model using the "two-cuff" technique introduced by Kamada has been well accepted since 1983, but the incidence of biliary complications remains extremely high, there is an urgent need to improve the technology for biliary reconstruction.

Innovations and breakthroughs

Most previous studies used the "two-cuff" technique to establish rat liver transplant models, but few focused on the high incidence of biliary complications. In view of the experience in over 600 cases of rat orthotopic liver transplantation in this study, biliary complications are almost inevitable by using the classical "two-cuff" technique.

Applications

More attention should be paid to the occurrence of biliary complications in ROLT model. The established mode of hepatic artery and biliary reconstruction should be modified.

Terminology

Biliary complications: often include hilar abscess, intrahepatic and extrahepatic biliary dilatation, biliary sludge. "Two-cuff" technique: A classical method used in rat liver transplantation, which was first introduced by Kamada *et al*. The key steps are: Portal vein and infrahepatic inferior vena cava are induced through the cuffs and the distal end of the vein is completely reversed and fixed onto the cuff with a 5-0 silk ligation.

Peer review

The paper is well designed and the experience is valuable to be published.

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