The preliminary studies on prevention of TIPSS shunt stenosis with ^{103}Pd stents

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Abstract To evaluate the role about prevention of shunt stenosis after transjugular intrahepatic portosystemic stent shunt (TIPSS) by ^{103}Pd stents, ^{103}Pd stents and general stents are placed respectively in 18 healthy swines after TIPSS. Angiography, pathological dissection and inspection of lumen area by light microscope are made respectively in the two groups at 4 and 8 weeks after TIPSS. Portal angiography showed that stenosis occured in 2 cases of the radiation group and 3 cases in the control group at 4 weeks. Occlusion was found in all of the radiation group and part stenosis appeared in 2 cases of the radiation group and 3 cases in control group at 4 weeks. Occlusion existed in all of the radiation group and part stenosis appeared in the control group at 8 weeks. Thickness of vascular wall of hepatic vein segment in scope of stents is (3.64±1.01) mm for the radiation group (12.95MBq) and (2.24±1.02) mm for the control group. Difference between two groups is evidenced (p<0.05). 9.25~12.95MBq ^{103}Pd stents can not prevent stenosis after TIPSS.

Keywords ^{103}Pd stents, Radiotherapy, TIPSS, Stenosis

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1 Introduction

Transjugular intrahepatic portosystemic stent shunt (TIPSS) is a new interventional technique widely used in clinical practice in recent decade. The metal stent is placed between hepatic vein and portal vein to make an artificial shunt and make blood in the portal vein into the systemic circulation. It effectively decreases the pressure of portal vein and attains the aim of treating bleeding of upper digestive tract and stubborn ascites. Clinically successful rate is 91.5%~100%. The effective rate is above 90%. Shunt stenosis and occlusion, however, occur after operation. Stenosis rate is high, 25%~80% in one year. Stenosis becomes a serious problem that influences the therapeutic effects in the middle and late stages after TIPSS. In animal experiments and clinical practice, coated stent may prevent fibrous hyperplasia in the shunt and raise the open rate. But the stenosis at two terminals of shunt remains not to be solved. In this study, the stent labeled with ^{103}Pd emitting γ radiation was used in the model of swine TIPSS to investigate its preventive effect on shunt stenosis after TIPSS.

2 Materials and methods

2.1 Experimental devices

(1) Transjugular Liver Access Set (RUPS-100, Cook Incorporated, USA); 5F angiographic catheter (Cook Incorporated, USA); φ= 8 mm Sacculus Dilatation Catheter (Cook Incorporated, USA); 1.27×10^{-3}m wire guide TFE coated amplatz extra stiff catheter exchange.

(2) The stents used in the experiment were distended stainless steel Z type stents (60mm × 10mm ~70mm × 10mm). The stents labeled with ^{103}Pd were made with chemical electroplating in Isotope Institute of China Atomic Energy Academy. The activity of ^{103}Pd on the stents can be confirmed according to ^{103}Pd content and electroplating time in electroplating

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liquid and was divided into two groups (9.25MBq and 12.95MBq).

2.2 Experimental animals

24 pigs (8~12 weeks, weighing 23~26kg, provided by Experimental Animal Department of China Medical University) were randomly divided into the radiation group (6 pigs for 9.25MBq and 6 pigs for 12.95MBq) and the control group (12 pigs). Each group is divided into 2 subgroups according to the time of taking specimen.

2.3 Establishment of model of swine TIPSS

(1) The pigs were anesthetized with given ketamine (30mg/kg, intramuscular injection) and 846 (10 mg/kg, intramuscular injection).

(2) Right jugular puncture was carried out with a 22G needle and a super-smooth wire (0.9 in diameter) was introduced into the inferior vena cava. Under X-rays, the hepatic puncture device (RUPS-100) was introduced along the wire.

(3) Portal puncture and portal angiography was carried out through hepatic vein or inferior vena cava. The catheter was introduced into right hepatic vein which was punctured and into the bifurcation of the portal vein and then replaced with 5F angiographic catheter. Then the contrast agent was injected, and the branches of the portal vein were observed and photographed.

(4) After introduction of a balloon catheter ($\varphi = 8$ mm) along the wire and dilating the puncture pathway, heparin (4000u) and gentamycin (160,000u) were injected.

(5) The stents compressed in the long sheath (RUPS-100) were transferred into the intra-hepatic shunt along the course above. After the orientation, the stents were released to make two ends of the stent extend into the portal and hepatic veins.

2.4 Management after operation

The pigs were fed with ordinary food, and heparin (3000u) was intramuscularly injected daily to continue anticoagulant treatment, the whole period lasted 7 days. According to the experimental design, the two groups were checked at 4 weeks and 8 weeks respectively.

2.5 Portal angioplasty

Portal angioplasty was examined at 4 and 8 weeks respectively. After anesthesia, a middle longitudinal incision (15~20 cm in length) was made, the skin, subcutaneous tissue, muscular layer and peritoneum were respectively cut and the liver was exposed. The hepatic vein was punctured with a 22G needle and a wire was introduced into portal trunk under X-rays, and then the wire was replaced with a 5F catheter for angioplasty to perform portal angioplasty to observe flow of shunt and take photos.

2.6 Pathological observation

The pigs were sacrificed with PBS perfusion, and the liver was isolated, with the shunt from portal vein to inferior vena cava being preserved. After the liver was fixed with 10% formalin for at least 24 hours, the stent along shunt was longitudinally opened, the surface within shunt was observed. Then the end of the portal vein, hepatic parenchyma and hepatic vein (or inferior vena cava) of shunt were transversely opened to take the metal wire out, each segment of the specimens was cut into several tissue blocks 5 mm in thickness, which were embedded with paraffin and sectioned continuously, the sections were stained with hematoxylin and eosin and observed under microscope.

2.7 Light microscopic examination

In order to judge the tissue hyperplasia in two groups, three sections in each segment (from three parts) of shunt were selected. After hematoxylin and eosin staining, the average thickness of proliferative tissue in each part was measured with light microscope and computer image analysis system (Knotron IBAS2.0). The data in the same stage between two groups were compared.

2.8 Statistics

t-test was used to compare the data ($x \pm s$) between two groups.

3 Results

3.1 Angiography

The portal angiography instantly made after operation showed that the shunt was well-opened. The result of portal angiography for 5 animals at 4 weeks showed that there was shunt stenosis in 2 cases in the radiation group (12.95MBq) and 3 cases in the control group. The results for 4 cases (2 cases in each group) at 8 weeks showed that 3 cases had no blood passing through and 1 case presented with shunt stenosis.

3.2 Pathological dissection

(1) White proliferative tissue was in the lumen of shunt in 3 cases at 4 weeks in the radiation group. After 8 weeks the venous end of stent for 1 case (12.95MBq) had extended to hepatic tissue which resulted in occlusion due to rapid growth, while in other 2 cases there was staining of bile on the surface of shunt near the portal vein and the hepatic segment of shunt within the hepatic parenchyma became black due to the closing of the lumen.

(2) Four weeks after operation, in one case of the control group, we found that the shunt was closed due to the proliferative tissue at the end of portal vein, surface of the shunt was stained with bile, and small amount of thrombi and proliferative tissue could be seen in the shunt; while in another case, a large amount of thrombi was observed within the shunt, and the lumen was completely closed. Eight weeks after operation, the white tissue covered the surface of the shunt and protruded into the shunt, and lumen was obviously induced to stenosis of lumen in one case; while in another case, the shunt was closed, the lumen was filled with brown tissue, and the yellow bile was seen on the surface of the shunt of the portal vein.

3.3 Light microscopy

(1) In the radiation group, epithelial proliferation of bile duct was found in 1 case, while in other 3 cases, the proliferation of the collagen fibers and fibroblasts, and infiltration of lymphocytes and neutrophiles with in and outside the shunt, especially around the wire were found, but the thrombi within the lumen were not found.

(2) In the control group, proliferative tissue and infiltration of neutrophil were found within and outside the shunt for 5 cases, thrombus was formed in 3 cases, and the epithelium of bile duct and bile staining were found in the end of the portal vein for 2 cases.

(3) Thickness measurement of proliferative tissue: at 4 weeks, the average thickness of the shunt of portal vein and hepatic vein for the radiation group (12.95MBq) was greater than that for the control group (p<0.05). The results measured were listed in Table 1.

Table 1 Comparison of thickness of proliferative tissue in various segments within stent (x±s)

Part	Dosage	4 weeks after			8 weeks after		
	(MBq)	^{103}Pd group	Control group	t	^{103}Pd group	Control group	t
HVE	9.25	3.77±1.21	2.35±1.24	2.0076	3.62±1.20	2.48±1.31	1.5718
	12.95	3.64±1.01*	2.24±1.02	2.3891	3.70±1.18	2.57±1.34	1.5503
HCE	9.25	3.84±1.02	2.51±1.18	2.0415	3.81±1.54	2.47±1.41	1.5720
	12.95	3.80±1.40	2.41±1.10	1.9122	3.78±1.06	2.58±1.26	1.7852
PVE	9.25	3.71±1.20	2.89±1.27	1.2898	3.75±1.12	2.86±1.30	1.2204
	12.95	3.68±1.05*	2.13±1.32	2.2509	3.65±1.08	2.78±1.08	1.3953

* Compared to the control, p<0.05

4 Discussions

The animal experiments on the intracoronary radioactive stent in recent years have confirmed that low energy γ radiation or β radiation can kill smooth muscle cells when they are in rapid growth and inhibit hyperplasia of new intimal formation to reach the aim of preventing vascular restenosis.[2,3] Nowadays, the nuclides commonly used are ^{32}P, ^{188}Re (emitting β radiation), and ^{192}Ir (emitting γ radiation). Waksman et al[4] used the balloon catheter containing low dosage of ^{192}Ir (35~140kGy) to radiate the intima of injured

swine coronary artery, showing that the extents of the intimal proliferation obviously decreased with the increase of the absorbed amount of the tissue.

Albiero et al[5] treated 122 cases of patients with stenosis of coronary artery using stents with three different levels of ^{32}P. After six months, the neointimal proliferation in these three groups of stent decreased with the increase of radioactive level (from 28kBq to 74kBq). But the restenosis rates at two ends of these stents were up to 41%~52%. The anthors called it "candy wrapper", and assumed that it was related to the sharp decrease of the radioactive level at terminals.

Many researches on the inhibition of coronary stenosis treated with radioactive stent have been reported. But reports on prevention of shunt stenosis of TIPSS with radioactive stents have not been found. Our study used the stent labeled with ^{103}Pd, which emits γ radiation (with half-life of 19d and energy of 23keV), for TIPSS and the features of shunt stenosis of TIPSS at different radioactive levels were observed.

In contrast to vascular stent, TIPSS is established through the connection of hepatic vein with portal vein and through the support of hepatic tissue. The repairing reaction of the blood vessels at two ends of the stent and the tissue around shunt is inevitable. Not only exists fibrous tissue in the liver, but also hyperplasia of the vascular intima occurs, which induces stenosis of shunt.

Contrary to predicted results, there was occlusion induced by fibrous hyperplasia in TIPSS treated with ^{103}Pd. Compared to the control, the features of shunt stenosis in the ^{103}Pd group are as follows: (1) occlusion induced by fibrous hyperplasia mainly occurred at the ends of the portal vein and right hepatic vein, and no obvious stenosis and occlusion were observed in the segments in the hepatic parenchyma of the shunt; (2) the tissue of the occluded shunt in ^{103}Pd group showed marked fibrous hyperplasia and inflammatory cells but no thrombosis, while thrombosis was observed in the control group; (3) the fibrous hyperplasia at the stenosis of TIPSS in the ^{103}Pd group was higher than the control, and the difference was significant for the segments of hepatic and portal veins (12.95MBq) ($p<0.05$) at 4 weeks.

The effect of "candy wrapper" is related to the sharp decrease of radioactive level at two ends of the stent. But the proliferative peak is at 4 weeks, different from 2 weeks for coronary stent described by Waksman[4], which may be related to the thick arterial intima, venous structure and the feature of venous proliferation.

Results in this study show that the ^{103}Pd stents with 9.25MBq and 12.95MBq can not inhibit the shunt stenosis. This may be attributed to the inadequate dosage which is lower than those in the coronary (14.8MBq) and bile duct stents (125.8MBq). The dosages used here are hard to suppress the repairing reaction of the tissue at two ends of the stent after injury, and may stimulate over-proliferation of the tissue. But the real mechanism still needs further studying.

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