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ORIGINAL ARTICLE

Magnetic Anastomosis Rings to Create Portacaval Shunt in a Canine Model of Portal Hypertension

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Abstract

Purpose This study evaluated a novel magnetic compression technique (magnamosis) for creating a portacaval shunt in a canine model of portal hypertension, relative to traditional manual suture.

Methods Portal hypertension was induced in 18 dogs by partial ligation of the portal vein (baseline). Six weeks later, extrahepatic portacaval shunt implantation was performed with either magnetic anastomosis rings, or traditional manual suture ($n = 9$, each). The two groups were compared for operative time, portal vein pressure, and serum biochemical indices. Twenty-four weeks post-implantation, the established anastomoses were evaluated by color Doppler imaging, venography, and gross and microscopic histological examinations.

Results Anastomotic leakage did not occur in either group. The operative time to complete the anastomosis for magnamosis (4.12 ± 1.04 min) was significantly less than that needed for manual suture (24.47 ± 4.89 min, $P < 0.01$). The portal vein pressure in the magnamosis group was more stable than that in the manual suture group. The blood ammonia level at the end of the 24-week post-implantation observation period was significantly lower in the magnamosis group than in the manual suture group. Gross and microscopic histological examinations revealed that better smoothness and continuity of the vascular intima had been achieved via magnamosis than with manual suture.

Conclusion Magnamosis was superior to manual suture for the creation of a portacaval shunt in this canine model of portal hypertension.

Keywords Magnetic compression technique · Magnamosis · Portacaval shunt · Portal hypertension · Canine model

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Introduction

The establishment of non-suture vascular anastomosis using magnet rings was first described by Oboral et al.[1] in 1978. Thereafter, the magnetic compression technique has been applied in various surgical procedures, including gastrointestinal anastomosis,[2,3] choledochojejunostomy,[4–6] vascular anastomosis[7–9], esophageal atresia,[10] and biliary strictures.[11–13] In 2009, Jamshidi et al.[14] coined the term magnamosis to represent magnetic compression anastomosis.

Surgical shunts have an irrefutably important role in the management of recurrent variceal bleeding in patients with portal hypertension.[15] Currently, traditional manual suture is used for the creation of surgical shunts, and this is a time-consuming and highly technical method. In this paper, we test the application of magnetic anastomosis rings for creating a side-to-side portacaval shunt in a canine model of portal hypertension, in comparison with traditional manual suture.

Methods

The Committee on the Ethics of Animal Experiments of Xi'an Jiaotong University (permit number 2010-105) approved the study protocol.

Dogs and Their Treatment

Twenty male beagles, aged > 1 year and weighing 12–18 kg, were obtained from the Experimental Animal Center, College of Medicine, Xi'an Jiaotong University (Xi'an, China). The protocol was designed to minimize pain or discomfort to the dogs. All the dogs were treated in a humane manner, in compliance with the Guide for the Care and Use of Laboratory Animals of Xi'an Jiaotong University Medical Center.

The dogs were acclimatized to laboratory conditions (23 °C, 12 h/12 h light/dark, 50% humidity) and provided access to food and water ad libitum for 2 weeks prior to the start of the experiments.

Magnetic Anastomosis Rings

Briefly, the magnetic anastomosis device comprises two parent rings and two daughter rings (Fig. 1a; Table 1). The parent rings are ladder-like elliptical rings, made of pure iron and coated with titanium nitride. The daughter rings are elliptical rings of neodymium-iron-boron (NdFeB, N45) permanent magnet and coated on the surface with nickel. The magnetic anastomosis rings were manufactured by the Northwest Institute for Nonferrous Metal Research (Xi'an, Shaanxi Province, China). The four parent and daughter rings were matched in two pairs (Fig. 1b) that attract to form two magnetic pairs (Fig. 1c). For the creation of the portacaval shunt, two pairs of the anastomosis rings are required (Fig. 2).

Canine Model of Portal Hypertension

For the induction of portal hypertension, the dogs were anesthetized by administration of an intraperitoneal injection of sodium pentobarbital (30 mg/kg body weight). To avoid postoperative infection, prophylactic benzylpenicillin sodium was administered intravenously at 100,000 U/kg body weight, 30 min before surgery.

A 5-cm midline abdominal incision was made. The portal vein was exposed, and the tissue surrounding the distal portion of the portal vein was dissected. An indwelling catheter was placed in the right gastroepiploic vein to monitor the portal vein pressure. A 1-0 non-absorbable surgical suture (Aipu Medical Products, Hangzhou, China) was placed beneath the portal vein and ligated to achieve partial ligation of the portal vein, until the portal vein pressure increased to 2.5-fold that recorded before ligation (i.e., baseline). The abdominal incision was closed in layers.

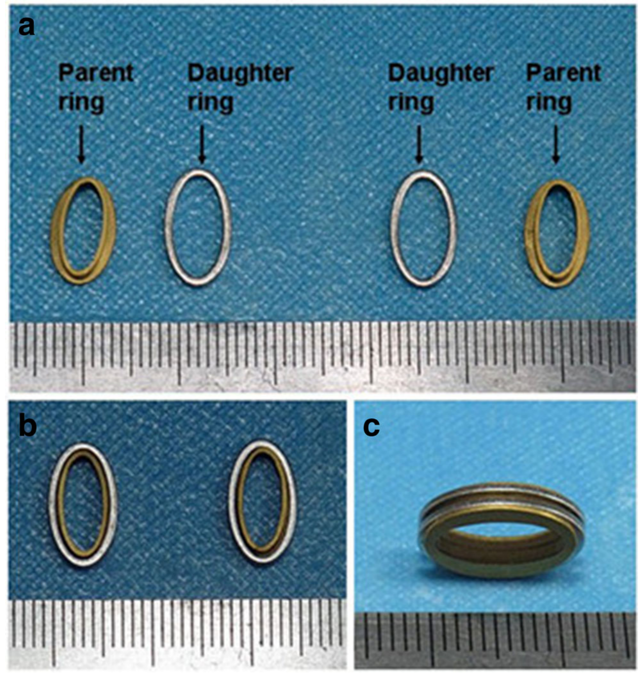

Fig. 1 The magnetic anastomosis device. **a** The functional part of the magnetic anastomosis device is composed of two parent rings and two daughter rings. **b** The daughter ring and parent rings attract and are matched into a pair. **c** When the two daughter rings attract, the anastomotic channels are established

After the animals recovered from the anesthesia, they were provided food and water. The prophylactic administration of benzyl penicillin sodium as intramuscular injection of 100,000 U/kg body weight was continued, once every 12 h for 3 days after the operation.

Six weeks after ligation of the partial portal vein, the portal vein pressure was measured again. If the portal pressure at this measurement was more than 1.5-fold the baseline level, it was

Table 1 Parameters of the parent and daughter ring

		Daughter ring	Parent ring
Material		N45 NdFeB	Pure iron
Weight, g		0.186	0.240
OD axis, mm	Major	13.2	11/13.2*
	Minor	7.2	5/7.2*
ID axis, mm	Major	11.2	10
	Minor	5.2	4
Thickness, mm		1	1.5/2*
MFD, mT		130	0

*Ladder part/total

ID, inner diameter; *MFD*, magnetic flux density; *OD*, outer diameter

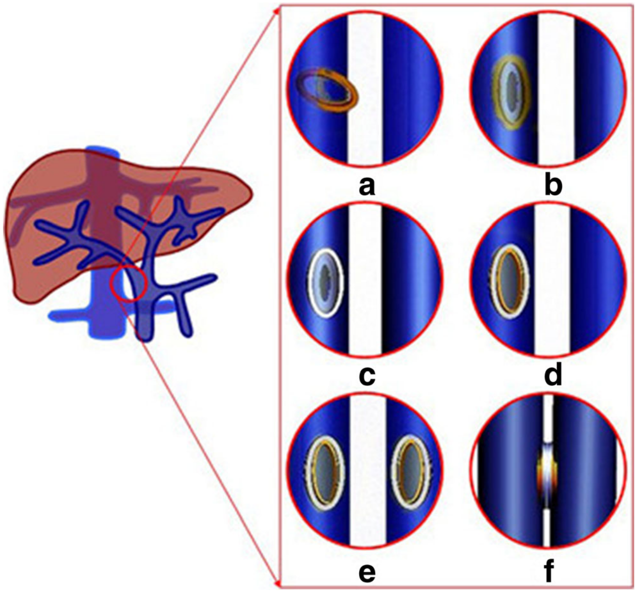

Fig. 2 Diagram of the side-to-side portacaval shunt. (**a**) Inferior vena cava incision and inset of the parent ring into the inferior vena cava (IVC). (**b**) Adjusting the parent ring in the proper position. (**c**) The daughter ring is placed in the extravascular space and the parent and daughter rings attract. (**d**) The vascular wall covering of the anastomosis ring is removed. (**e**) The same method is used to establish magnetic anastomosis in the portal vein. (**f**) Attraction between both daughter rings and completion of the magnetic anastomosis channels

considered that portal hypertension was successfully established in the dogs. These dogs with portal hypertension were then equally apportioned to 2 groups according to randomized number assignment. Side-to-side portacaval shunt implantation was then performed on the 2 groups, respectively using either magnamosis (study group) or the traditional manual suture (control).

Side-To-Side Portacaval Anastomosis

Twelve weeks after the initial ligation surgery, another procedure was undertaken for the creation of a side-to-side portacaval anastomosis. The initial incision was extended to reach a length of 12 cm. The portal venous pressure was measured through the gastric coronary vein. Dogs that did not have portal venous pressure ≥ 1.5-fold that of the baseline measurement were excluded from the study.

Magnamosis

In the study group, side-to-side portacaval anastomosis was established with the use of the magnetic anastomosis rings. Briefly, the steps of the procedure are as follows: the portal vein and the inferior vena cava were exposed, and the surrounding tissue dissected. Approximately 15 mm of the portal vein was occluded temporarily by placing vascular clamps at the proximal and distal ends. A heparin sodium injection was administered (1 mg/kg) through the right great saphenous vein to prevent thrombosis.

Five minutes later, a 5-mm incision was performed on the middle part of the blocked region of the portal vein, and a parent ring was introduced into the portal vein (Fig. 2a). The position of the parent ring was adjusted to ensure that the ring was positioned at the center of the incision (Fig. 2b). One daughter ring was placed external to the portal vein but precisely aligned with the parent ring. Attraction between the parent and daughter rings was achieved, thereby holding the vessel wall in its place (Figs. 2c and 3a). The vessel walls covering the magnetic ring were removed, and a magnetic vascular port was created (Figs. 2d and 3b).

Using the same method, the other pair of magnet rings was placed in the inferior vena cava to create another magnetic vascular port, with its position adjacent to the portal vein port in the inferior vena cava (Figs. 2e and 3c). Subsequently, attraction between the two pairs of magnetic rings was completed, and a side-to-side portacaval

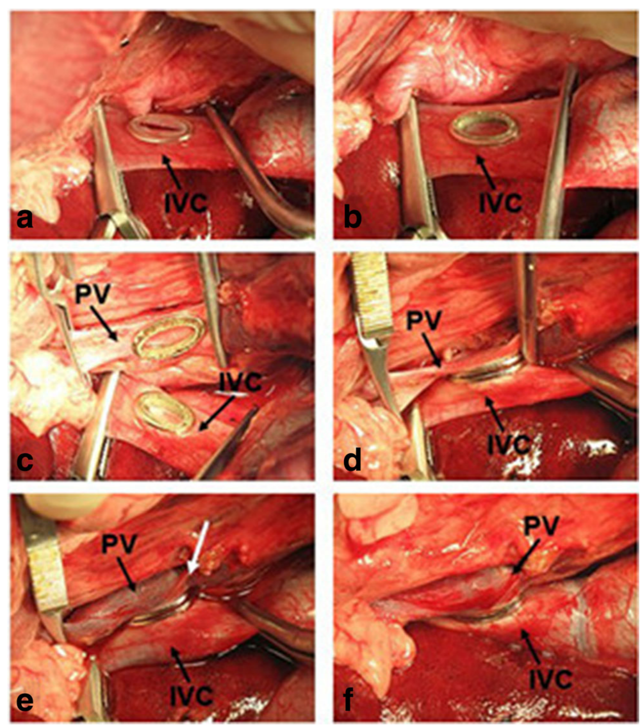

Fig. 3 Protocol for creation of the magnamosis shunt. **a** Parent and daughter rings placed in the inferior vena cava. **b** Vascular wall covering the anastomosis ring and the magnetic anastomosis port was established on the inferior vena cava. **c** The same method was used to establish magnetic anastomosis port in the portal vein. **d** Attraction between the two daughter rings, which completes the side-to-side portacaval shunt. **e** Vascular clamp on the distal portal vein (white arrow) was removed to check for leakage from the anastomosis. **f** Other vascular clamps were removed and the side-to-side portacaval shunt was established

anastomosis was established using magnamosis (Figs. 2f and 3d). Finally, the vascular clamps were released (Fig. 3e, f), and the abdomen was closed after measuring the portal venous pressure. After the dogs recovered from anesthesia, they were allowed unrestricted activity, individual runs, and normal feeding.

Manual Suture

In the control group, the traditional manual suture technique was used to establish side-to side portacaval shunting, as follows. After the portal vein was exposed, the surrounding tissue was dissected. With the same method, the inferior vena cava was exposed. Vascular clamps blocked the blood flow of the portal vein, and inferior vena cava on both ends of the anastomosis (Fig. 4a). An elliptical opening was created, with a major axis of 10 mm and minor axis of 4 mm, in both the portal vein and inferior vena cava (Fig. 4b). Side-to-side portacaval anastomosis reconstruction was then performed with continuous sutures using a 6-0 prolene wire (Ethicon; Johnson & Johnson, Somerville, NJ, USA) (Fig. 4c, d). The abdomen was closed after measuring the portal venous pressure.

Both groups were administered subcutaneous buprenorphine, as required, for pain relief. In addition, intramuscular benzyl penicillin sodium was administered for prophylaxis for 3 postoperative days. The dogs in the magnamosis study group were administered oral aspirin (50 mg; Bayer Schering Pharma AG) and warfarin sodium (2.5 mg; Shanghai Xinyi Jiufu Pharmaceutical) daily for 8 postoperative weeks.

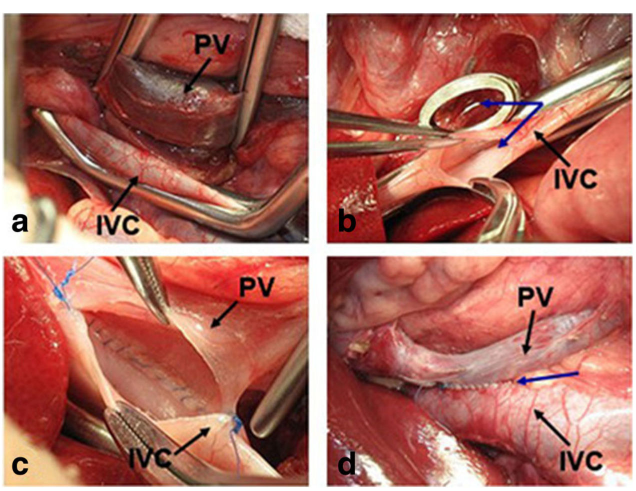

Fig. 4 Procedure of the manual suture technique. **a** Isolation and clamping of the portal vein and inferior vena cava. **b** Elliptical opening created on the side wall of the inferior vena cava, with its size being as large as the internal diameter of the parent ring (blue arrow). **c** Application of continuous suture in the anastomosis. **d** Establishment of the side-to-side portacaval shunt (blue arrow)

Patency Assessment and Portal Vein Pressure Measurement

Duplex ultrasound scanning (Philips 5500; 7-MHz linear probe) was performed 12 weeks after the ligation surgery, with the animals placed under sedation induced by administration of 1 mL medetomidine hydrochloride. Twenty-four weeks after the operation, portal venography was performed and portal vein pressure was measured.

Tissue Harvest

At the end of 24 weeks, the animals were anesthetized by the administration of sodium pentobarbital. The dogs were prepared for surgery and the patency of the anastomoses was examined by direct observation. The specimens of the side-to-side portacaval anastomoses were then harvested. After gross observation, some samples were obtained, fixed in 10% formalin at pH 7.0, and processed in accordance with standard histological procedures. Sections (4-μm thickness) were stained with hematoxylin and eosin as well as Masson trichrome stain for observation under a light microscope.

Another set of samples was fixed in 1% glutaraldehyde. They were then sputter-coated with gold-palladium and photographed under a scanning electron microscope (Model JEOL 200, Niihon Denshi, Japan).

Statistical Analysis

Results are expressed as mean ± standard deviation. Intergroup differences were analyzed with the independent samples' *t* test, the Mann-Whitney *U* test, and Fisher's exact test. A P value < 0.05 was considered statistically significant.

Results

Portal Hypertension Model

We were able to induce portal hypertension successfully in 18 of the 20 dogs, as per the criteria of a 1.5-fold increase in the baseline portal venous vein pressure at 6 weeks after partial portal vein ligation. The remaining two dogs were therefore excluded from subsequent analysis, and nine dogs were apportioned to each of the study and control groups.

Operative Time

The side-to-side portacaval anastomosis was successfully established in all of the 18 dogs, and all dogs survived the surgery. The time for completion of the portacaval anastomosis was 4.12 ± 1.04 min (3–6 min) in the magnamosis group.

The time required for the procedure in the manual suture group was 24.47 ± 4.89 min (19.5 to 32.8 min; Fig. 6b).

Imaging Examination

All the dogs underwent color duplex Doppler scanning at 12 weeks after the creation of the shunt. Ultrasonographic examination was also performed, which revealed that there was no shunt blockage in the magnamosis group (Fig. 5a). Portal vein angiography performed 24 weeks after creation of the shunt showed uninterrupted flow of the contrast media from the portal vein to the inferior vena cava in all the dogs, indicating that none had developed thrombosis or stenosis (Fig. 5b, c).

Portal Vein Pressure

The portal vein pressure was measured to confirm the effect of the portacaval shunt. At baseline, i.e., before partial ligation, the portal vein pressures of the magnamosis and manual suture groups were comparable (12.44 ± 1.81 and 12.67 ± 2.06 cmH_2O, respectively). At the end of 6 weeks, these values had increased to 22.67 ± 3.81 and 22.44 ± 3.71 cmH_2O ($P >$ 0.05) and remained stable. Twenty-four weeks after the completion of the side-to-side portacaval shunt, the portal vein pressure had reduced to 13.56 ± 1.74 cmH_2O in the magnamosis group, and 10.89 ± 1.36 cmH_2O in the manual suture group ($P < 0.01$; Fig. 6a).

Blood Biochemical Examination

Blood biochemistry tests were performed to compare the effects of the two methods of shunt creation on liver function. The results of the tests revealed no significant deviation in liver function after the establishment of portal hypertension.

In the magnamosis group, no differences were noted in the pre-and post-shunt liver function parameters. However, in the control group, aspartate transaminase significantly increased after creation of the shunt, while the changes in the levels of the total protein and albumin were not significant.

Blood ammonia values before the shunt were comparable between the magnamosis group (44.22 ± 19.31 μmol/L) and manual suture group (39.67 ± 9.33 μmol/L). At the end of 24 weeks, the blood ammonia of the magnamosis group (47.44 ± 16.41 μmol/L) was significantly less than that of the manual suture group (65.78 ± 10.49 μmol/L; $P < 0.01$; Fig. 6c, d).

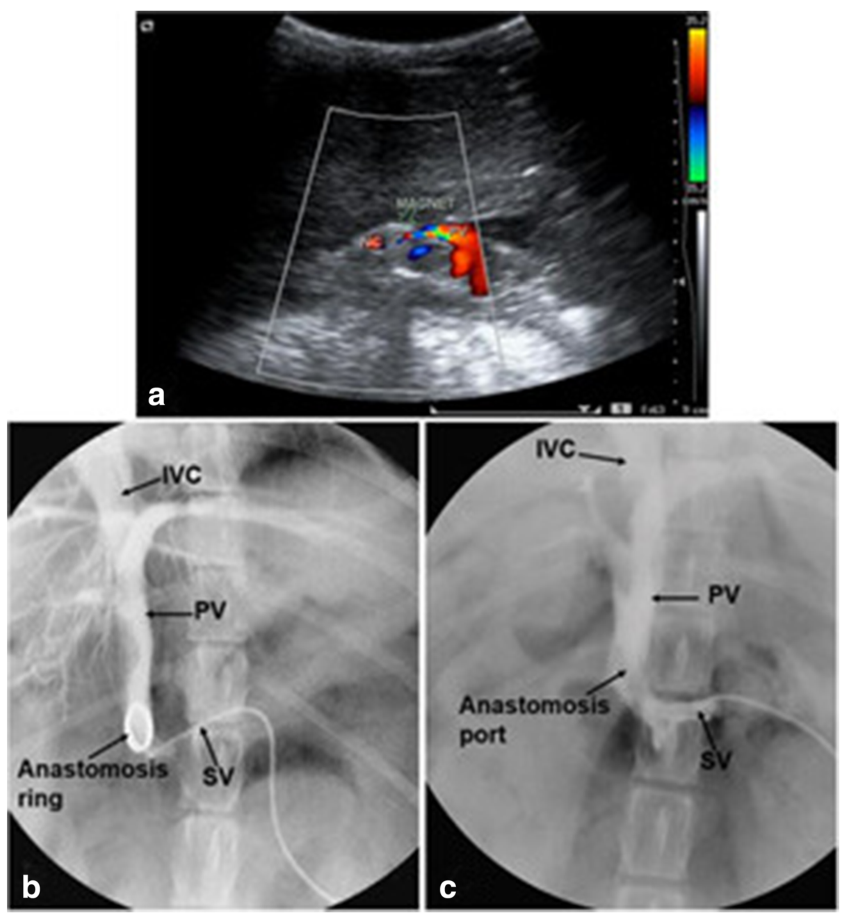

Fig. 5 Vascular ultrasound and portal vein angiography. **a** Ultrasonographic examination 12 weeks after portacaval shunt creation revealed no intraluminal stenosis in the shunt. **b** In the magnetic anastomosis group, portal vein angiography was performed 24 weeks after portacaval shunt creation, and the contrast media can be observed flowing from the portal vein into the inferior vena cava through the magnetic anastomosis ring. **c** In the manual suture group, portal vein angiography was performed 24 weeks after portacaval shunt, and the contrast media can be observed flowing from the portal vein into the inferior vena cava through the shunt

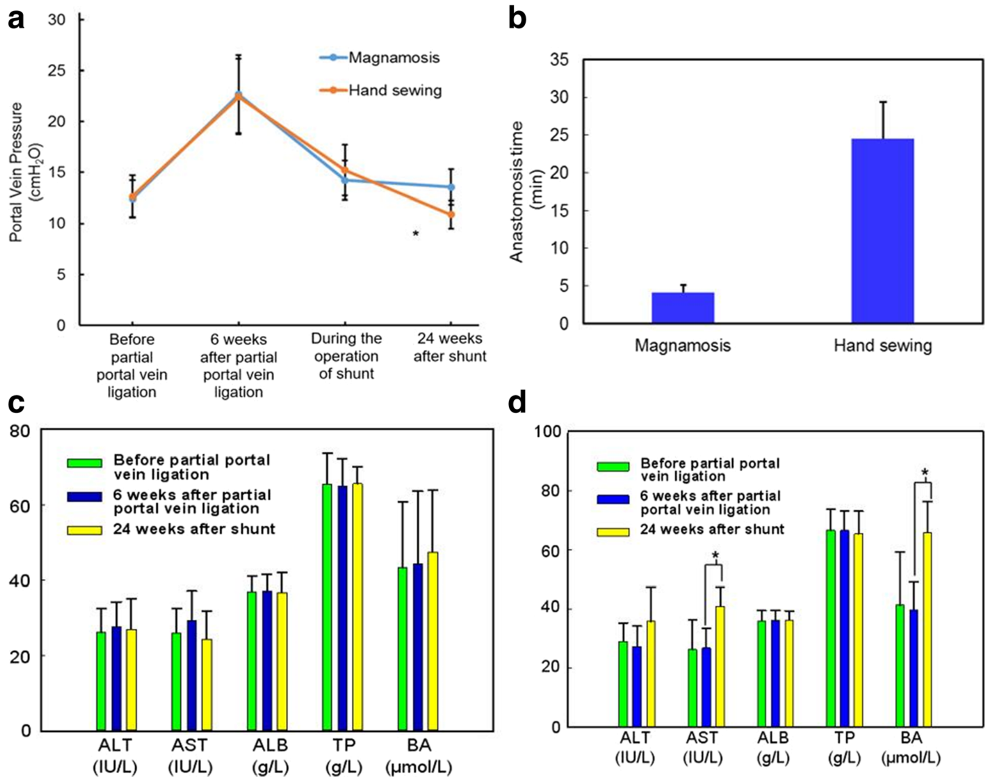

Fig. 6 Portal vein pressure and biochemical tests. **a** Changes of the portal vein pressure. *, $P < 0.01$, the portal vein pressure at 24 weeks after shunt creation compared with during the operation in the control group, $n = 9$. **b** Time required for completion of side-to-side portacaval shunt. *, $P < 0.01$, the magnamosis group compared with the manual suture group, $n = 9$. **c** Blood levels of ALT, AST, ALB, TP, and BA before and 6 weeks after partial portal vein ligation, or 24 weeks after shunt in the magnamosis group. **d** Blood levels of ALT, AST, ALB, TP, and BA before and 6 weeks after partial portal vein ligation or 24 weeks after shunt in the manual suture group. *, $P < 0.01$. Comparison of AST and BA before and 24 weeks after shunt implantation in the manual suture group, $n = 9$. ALT, alanine aminotransferase; AST, aspartate transaminase; ALB, albumin; TP, total protein; BA blood ammonia

Gross Appearance of Anastomosis

Significant differences were observed between the two groups in terms of gross appearance of the anastomotic specimens (Fig. 7a, b; Table 2). In the magnamosis group, the rings were covered by vascular intima internally and by fibrotic tissue externally, and therefore, the rings were not visible from either aspect. In the manual suture group, the sutures were visible from the internal aspect of the anastomosis, and the edges of the blood vessels were rough and uneven on the surface.

Histological Studies

Representative images of the hematoxylin and eosin-stained anastomotic stomas retrieved from the two groups at 24 weeks were taken (Fig. 7c–f). In the manual suture group, the sutures were visible beneath the intima at the site of the anastomotic stoma, and inflammatory cells were visible adjacent to the anastomotic stomas. Masson's trichrome staining revealed a large quantity of neatly arranged collagen surrounding the adventitia in the manual suture group.

In the magnamosis group, the vascular adventitia was contiguous from the portal vein to the inferior vena cava, and completely covered the inner surface of the parent ring.

Scanning Electron Microscopic Studies

Scanning electron micrographs of samples obtained from the magnamosis group revealed a smooth appearance of the endothelium on the luminal surface of the portacaval shunt (Fig. 8). The entire intravascular surface of the magnetic shunt appeared to be covered by a monolayer of endothelial cells; the endothelial cells were regularly aligned with the blood flow and exhibited a normal and uniform morphology. No obvious inflammatory reaction was noted in the shunt tissue.

In the manual suture group, the sutures were visible in addition to large folds of the anastomotic intima.

Discussion

Herein, we describe for the first time the use of magnamosis to create a portacaval shunt. Compared with other methods of

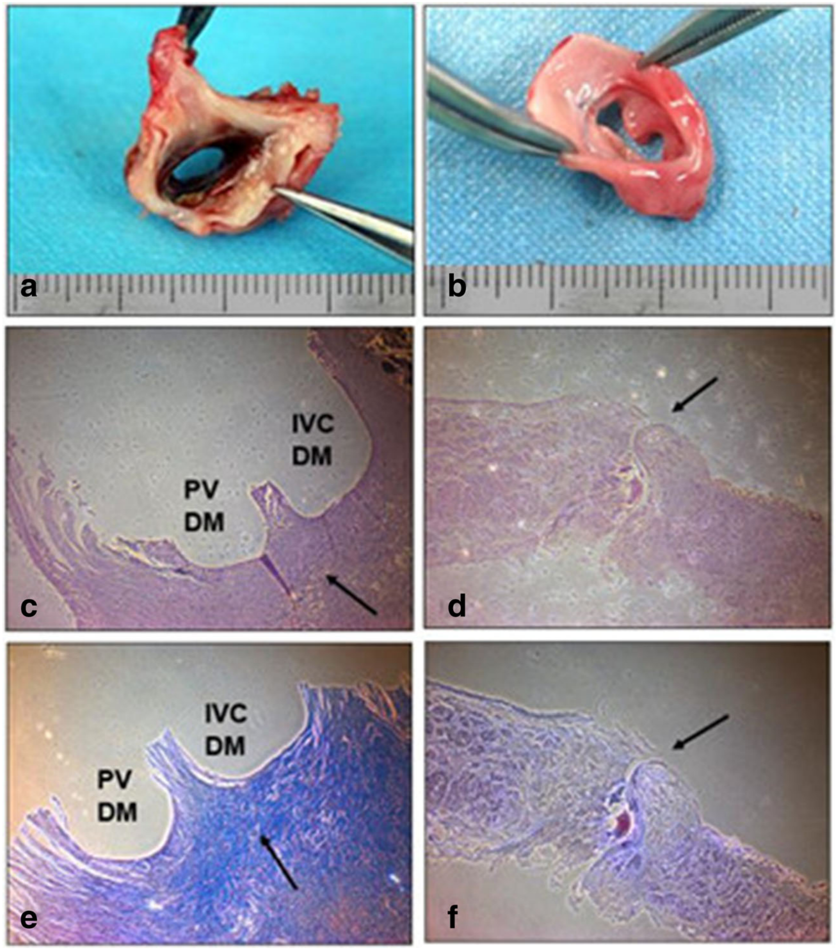

Fig. 7 Gross appearance and histology of the portal-inferior vena cava shunt. **a**, **b** Images of whole views comparing the side-to-side portacaval anastomoses between the magnetic anastomosis group and the manual suture group. Histological examination of shunt: (**c** and **e**) HE × 4, magnamosis group; (**d**) and (**f**) Masson × 4, manual suture group

anastomosis, this is a very different design in that the principles of magnetism are applied to establish anastomoses, without the need for suturing. This design is not only convenient for establishing vascular anastomosis, but also ensures that the vessel section does not come in direct contact with the blood, which allows for good patency.

One of the unique features of this method is the use of NdFeB for the preparation of daughter rings, which has many advantages. First, the NdFeB magnet is resistant to corrosion, non-toxic, and has good biological compatibility, which renders it safe for use in the human body and superior to permanent magnets made of other materials. [16]

Table 2 Size of shunt in the study and control groups[a]

		Length	Width
Expected size		10	4
Magnamosis	Actual	8.49 ± 0.23	3.60 ± 0.16
	Changing rate, % [b]	− 15.1	− 10.0
Manual suture	Actual	14.24 ± 0.76	6.86 ± 0.91
	Changing rate, % [b]	+ 42.4	+ 71.5

[a] $n = 9$, each group; [b] Compared with the expected size

Second, sintered NdFeB is a third-generation, rare-earth permanent magnetic material. Because of its outstanding properties and relatively low cost, NdFeB magnets are popular in the field of machinery manufacturing. Compared with other magnetic materials, NdFeB has superior magnetism, whereby even small sizes can be used effectively.[17]

In our technique, the use of pure iron for the parent ring ensures that the anastomosis is held firmly in place. The structure of the parent ring is more complex than the daughter, and pure iron was chosen for the parent ring, rather than NdFeB, to simplify the process. Both NdFeB and pure iron have good histocompatibility, but may be susceptible to corrosion by chemical agents. Consequently, we coated each of the rings with titanium nitride and nickel to ensure material stability and biocompatibility.

The 2009 updated guidelines of the American Association for the Study of Liver Diseases included the recommended use of covered, rather than bare, stents in the creation of the TIPS.[18] Thus, the use of expanded polytetrafluoroethylene-covered stents is now preferred, due to the lower risk of shunt dysfunction, and possibly better outcomes than those obtained with bare stents.[19,20] However, TIPS still cannot completely

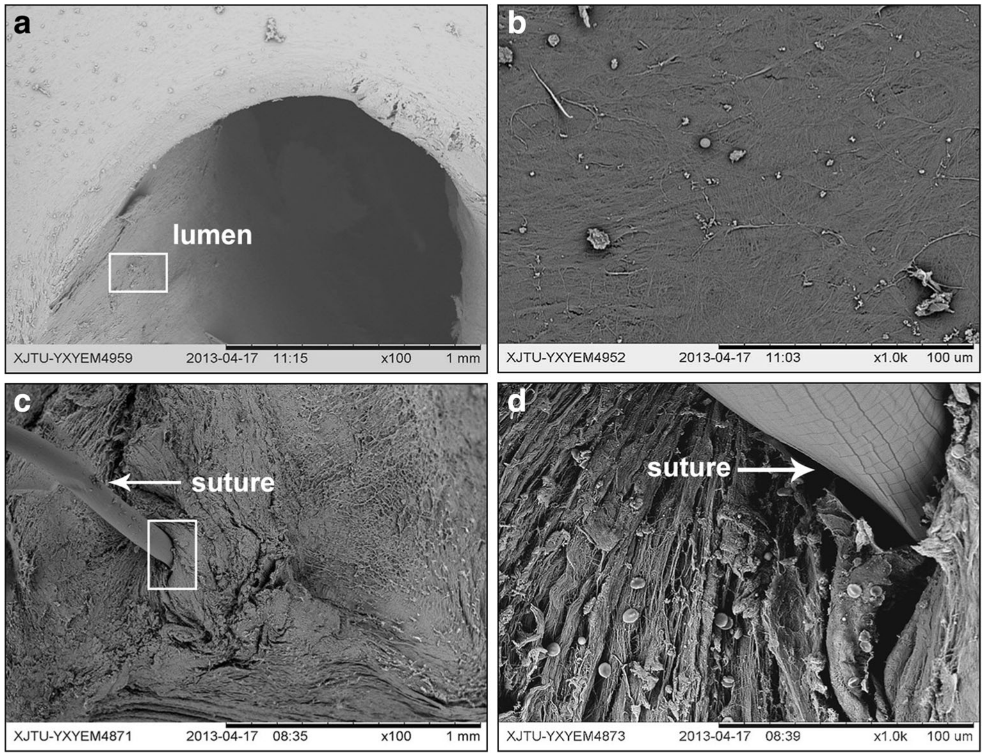

Fig. 8 Scanning electron microscopy of the portacaval shunt. **a**, **b** The intraluminal endothelium was smooth, and endothelial cells were regularly aligned with a normal and uniform morphology at the shunt in the magnamosis group. **c**, **d** A projecting suture from the intraluminal surface was visible and endothelial cells were vertically arranged and exhibited morphological diversity

replace the surgical shunt, which is the basis of the present investigation.

After implantation, the shunt expands, leading to a high incidence of hepatic encephalopathy. This is its biggest drawback. Prosthetic 8-mm HGPCS can effectively limit shunt expansion, thereby reducing the incidence of hepatic encephalopathy. However, the disadvantages include the high cost of artificial blood vessels, the need for manual suture of the vessel, the highly technical nature of the procedure, and the need for long-term use of anticoagulants.

On the other hand, the use of magnetic anastomosis rings to establish a portacaval shunt has the following three main advantages. First, during the procedure, the size of the anastomosis ring can be chosen according to the portal venous pressure of the patient. The shunt will remain patent and not become narrow, which will allow a stable flow over the long term. Therefore, it is a limited portacaval shunt. Secondly, with magnetic anastomosis rings, the portacaval shunt can be created in much less time (~ 4 min) compared with manual suture (~ 26 min). Finally, oral anticoagulant therapy with magnamosis is required for only a short period, unlike with HGPCS. About 6 weeks after the procedure, the vascular intima covers the inner surface of the parent ring and the anticoagulant can be discontinued.

What is the effect of allowing a metal foreign body such as the magnetic anastomosis ring to remain within the body permanently? The answers to this question can only be obtained through long-term clinical observation, but the clinical study by Klima et al. [21] may provide some insights. In addition, Klima et al. [22] used magnetic resonance imaging (MRI) to evaluate the safety of the MIDCAB, and suggested that MRI after MIDCAB is safe at any time of the operation, even during the very early period before the start of wound healing, when only the magnetic force maintains the anastomosis. In our present study, we did not determine whether magnetic anastomosis rings affect MRI scans.

Liver transplantation is the most effective treatment for portal hypertension. However, side-to-side portacaval shunts and H-graft portacaval shunts established via manual suture often lead to severe hilar tissue adhesions, which can complicate later liver transplantation. Application of the magnetic anastomosis ring for establishing portacaval shunts, which we report here, will minimize the formation of tissues adhesions, since operative time is shorter and the damage to the surrounding tissues is much less. Therefore, our technique could be beneficial for patients who are likely to receive liver transplantation at a later date.

To summarize, the use of magnetic anastomosis rings in the creation of side-to-side portacaval shunt shortens the operative time, maintains a high patency rate over the long term, prevents shunt expansion, and precludes the need for long-term anticoagulant use and liver transplantation. Although the results of this study are encouraging, large-scale longitudinal studies are necessary to confirm the effectiveness of this novel method to implement portacaval anastomosis.

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Performed the research and acquired the data: Hao-Hua Wang, Jia Ma, Shan-Pei Wang, Feng Ma, Jian-Wen Lu, Xiang-Hua Xu, Xiao-Peng Yan
Analyzed the data: Jian-Wen Lu, Xiang-Hua Xu, Xiao-Peng Yan
Manuscript writing: Hao-Hua Wang, Jia Ma, Yi Lv, Xiao-Peng Yan
Final approval of manuscript: All authors

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Compliance with Ethical Standards

The Committee on the Ethics of Animal Experiments of Xi'an Jiaotong University (permit number 2010-105) approved the study protocol.

Conflict of Interest The authors declare that they have no conflict of interests.

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