Experimental study of the effects of absorbable gelatin sponge and non-absorbable polyvinyl alcohol particle material used in transcatheter arterial embolization on liver tissues

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Abstract. Hepatic trauma is a leading cause of death in major abdominal trauma, and transcatheter arterial embolization has been widely used to treat it. However, there is limited research on whether absorbable gelatin sponge (AGS) and non-absorbable polyvinyl alcohol particles (PVA) have different effects on liver tissue, making it an important area of exploration. The present study investigated this issue using animal experiments by performing transhepatic arterial embolization with AGS and PVA. The effects on normal liver tissue in rabbits were examined by detecting liver function and inflammatory indexes, conducting histopathological examination, and using western blotting to detect apoptotic proteins. There were significant differences between the AGS and PVA groups after embolization. The AGS group exhibited a trend of improvement at ~1 week after embolization, and all indicators were statistically different until day 21 compared with the PVA group. The AGS group exhibited improved repair of hepatocytes and the biliary system based on H&E staining, while the PVA group exhibited more severe necrosis of the hepatocytes and biliary system around the embolization site. The western blotting results indicated that the Bcl-2/Bax ratio decreased on day 1 and day 3, and then rebounded in the AGS group on days 7 and 21, demonstrating gradual repair of hepatocytes compared with the PVA group.

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Introduction

Hepatic trauma is the leading cause of death in major abdominal trauma, and the incidence has increased considerably in the last three decades (1). Liver rupture injuries account for approximately 15 to 20% of abdominal injuries. According to results from clinical data, the mortality rate of hepatic trauma is about 10% and up to 50% in severe hepatic trauma or combined with other organ injuries (2,3). Hemorrhagic shock is the leading cause of death in hepatic trauma, making prompt and effective hemostasis the most critical task for the successful treatment of severe cases.

Previously, most patients diagnosed with hepatic trauma were treated surgically using techniques such as tamponade, liver repair, vascular ligation, and hepatectomy (4). However, with improvements in imaging quality and accessibility, as well as the development of percutaneous interventions, non-operative management (NOM) has become the primary method for treating severe hepatic trauma (5,6). The treatment concept for hepatic trauma has shifted, with nearly 80% of patients now preferring non-operative treatment (7). Transcatheter arterial embolization (TAE) has emerged as a highly effective non-surgical treatment for severe hepatic trauma due to its minimally invasive nature, precise visualization of the bleeding artery, precise hemostasis, and lower degree of operational difficulty. TAE has been widely performed, and its effectiveness has been clinically proven (8,9). However, while TAE can achieve effective hemostasis, some patients may experience postoperative liver pain, fever, and other complications related to hepatic ischemia and necrosis. These questions are worth exploring further (10-13). To address these questions, this study investigated the effects of transhepatic arterial embolization on normal liver tissues in rabbits by using an AGS and PVA, respectively. By better understanding the impact of these techniques, we can develop improved approaches for protecting the liver during hepatic intervention embolization, reducing complications, and improving the survival rate.

Materials and methods

Experimental animals and related materials. Experimental animals for this study were New Zealand white rabbits weighing

2-2.5 kg, obtained from Songlian Experimental Animal Farm in Songjiang District, Shanghai. The animal license number for this study was (SCXK (Shanghai) 2017-0008). Materials used in the study included PVA (100 μm) and 1.7F EV3 microcatheters purchased from COOK Corporation (Bloomington, IN, USA), an absorbable gelatin sponge purchased from Jinling Pharmaceutical Co. Ltd, and ELISA kits for TNF-α, IL-6, and SOD purchased from Jiancheng Institute of Biological Engineering (Nanjing, Jiangsu, China). Bcl2 and Bax antibodies were purchased from Proteintech Corporation (Inc., Chicago, USA).

Experimental animals and study design. This study received approval from the Animal Experimentation Committee of Xiamen University (XMULAC20230016), and all rabbits were treated in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. A total of 45 New Zealand white rabbits were carefully selected and randomly divided into three groups using the numerical table randomization method: a control group (5 animals), a PVA group (20 animals), and an AGS group (20 animals). The control group underwent no experimental manipulation (1 animal per time point), while animals in the experimental groups were evaluated at 1, 3, 7 and 21 days after embolization (5 animals per time point). To minimize the influence of biological rhythms on the experimental results, all experiments were conducted at 8 am. Two commonly used interventional embolic materials were chosen for the study: AGS for absorbable materials and PVA for non-absorbable materials.

Establishment of animal models. We established a rabbit embolism model by performing hepatic artery embolization using AGS and PVA embolic materials. The procedure for establishing the model was as follows: All rabbits were fasted for 12 h before surgery and could drink water freely. Anesthesia was administered by intramuscular injection(IM) of ketamine (25 mg/kg) and medetomidine (0.2 mg/mg) and maintained with 1-2% isoflurane (600 ml/min). A catheter (1.7F vascular sheath) was delivered via the femoral artery using Seldinger's technique, and then the catheter was selectively delivered into the celiac trunk, the common hepatic artery, and contrast agent was injected into the arterial DSA examination to reveal the hepatic artery course and branches. The 1.7Fcoaxial catheter was super-selectively cannulated into the left hepatic artery, and the embolic material was slowly injected, with 0.1 ml of AGS in the AGS group, 0.1 ml of PVA in the PVA group, and an equal amount of normal saline in the control group. After completion, the same imaging rate was used to understand the embolization (the end point of injection was paravalvular flow arrest). At the end of the operation, the tube was removed to stop the bleeding, the puncture site was dressed with pressure, and the right inguinal incision was sutured. After the interventional operation, intramuscular penicillin and gentamicin were injected for three consecutive days to prevent infection.

Sample collection and preservation. Open the ear marginal vein channel of the experimental rabbit and perform induction anesthesia by administering propofol of 1.25 to 2 ml (5 mg/kg) through auricular intravenous. The rabbit was then euthanized by injecting 20-30 ml of air through the auricular intravenous to obtain blood and liver tissue specimens. Venous blood samples were taken at different time points and collected in tubes containing EDTA. The samples were then centrifuged at 3000 rpm for 10 min, and the resulting serum was stored at -80˚C. Following dissection, approximately 200 mg of liver left outer lobe tissue was immediately collected and gently rinsed in 5 ml of PBS for histopathological studies. The remaining tissue was frozen in liquid nitrogen and stored at -80˚C until tissue testing was performed.

Liver function and inflammatory indexes. In the control group, blood was collected immediately after euthanasia, while in the experimental group, blood was collected at 1, 3, 7, and 21 days after embolization, respectively. After centrifugation, serum was collected and analyzed using enzyme-linked immunosorbent assay (ELISA) to measure ten indicators of liver injury, including glutamate transaminase (ALT), glutathione transaminase (AST), alkaline phosphatase (ALP), bilirubin (BIL), albumin (ALB), r-glutamine transpeptidase (r-GT), SOD, CRP, TNF-a, and IL-6. The content changes of these ten indicators were monitored at the four time periods in the rabbit embolism model.

Histo-pathological examination. Immediately after euthanasia, the left outer lobe of the liver tissues from both control and experimental rabbits were collected, fixed with formaldehyde, embedded in paraffin, and sectioned. The sections were then stained with hematoxylin and eosin (HE) and observed under a microscope at 100x and 400x magnification. Images were captured for further analysis.

Western blotting. The Western Blot method was used to detect Bcl2 and Bax proteins in hepatocytes and biliary epithelial cells in liver tissue. To separate protein samples by electrophoresis based on molecular protein weight, 10% or 12% SDS-PAGE gel was prepared. The separated proteins on the gel were transferred to a polyvinylidene fluoride (PVDF) membrane by electrotransfer. After electrotransfer, the PVDF membrane was immersed in a blocking solution containing 5% skim milk powder and incubated at room temperature for 1 h. The corresponding primary antibodies, Bax and Bcl2, were added after washing the membrane with phosphate-buffered saline with Tween 20 (PBST) and incubated overnight at 4˚C. The corresponding horseradish peroxidase-labelled secondary antibody solution was added after washing the membrane with PBST and incubated for 1 h at room temperature. The PVDF membrane was then reacted with freshly prepared enhanced chemiluminescent agent (ECL) solution for 2 min and quickly exposed to a film in a dark room for development.

Statistical analysis. The statistical analysis was performed using SPSS version 27.0 and GraphPad Prism version 8.0 software. The measurement data were presented as mean ± standard deviation (s). To compare the differences among multiple groups, we used one-way analysis of variance (ANOVA), followed by post-hoc testing using Dunnett's method. Within the same group, we used paired sample t-tests to compare the differences among different time points. $P<0.05$ was considered statistically significant.

Results

Changes in liver function at different time periods in each group. On day 1, the PVA-treated group showed increased levels of Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Gamma-glutamyltranspeptidase (γ-GT), as well as significant increases in Alkaline phosphatase (ALP), Albumin (ALB), Bilirubin (BIL), C-Reactive protein (CRP), Tumor necrotic factor (TNF-α), and Interleukin-6 (IL-6) levels, and a significant decrease in Superoxide dismutase (SOD) levels. The AGS group also showed increased levels of ALT, AST, γ-GT, ALP, ALB, BIL, CRP, TNF-α, and IL-6, and a significant decrease in SOD levels. ALP and ALB levels were significantly different between the two groups on day 1.

On day 3, the PVA-treated group showed significant increases in ALT, AST, γ-GT, ALB, TNF-α, and IL-6 levels, while ALP and BIL levels decreased. The AGS-treated group showed significant increases in ALT, AST, γ-GT, ALP, ALB, and IL-6 levels, while BIL and CRP levels had some decreases. AST and TNF-α levels were statistically different between the two groups on day 3.

On day 7, the PVA-treated group showed decreased levels of ALT, AST, ALP, BIL, ALB, and γ-GT, and significant decreases in TNF-α and IL-6 levels, while the AGS-treated group showed decreases in ALT, AST, ALP, BIL, ALB, γ-GT, and CRP, and significant decreases in TNF-α and IL-6 levels, but a significant decrease in SOD levels. ALT, AST, CRP, TNF-α, and IL-6 showed statistical differences between the two groups.

On day 21, the PVA-treated group showed a certain decrease in the contents of ALT, AST, ALP, BIL, ALB, and γ-GT, and a certain increase in SOD levels, while the AGS-treated group showed a certain decrease in the contents of ALT, AST, ALP, BIL, ALB, and γ-GT, as well as significant decreases in TNF-α and IL-6 levels, and a certain increase in SOD levels. The liver biochemical indexes were statistically different on day 21 (Fig. 1).

HE staining. Observation of HE staining of liver sections at different time points in the AGS group and the PVA group revealed the following findings. In the AGS group, on day 1, the hepatocytes were swollen with fixed nuclei, the hepatic blood sinuses were dilated, and the bile duct epithelium mildly degenerated. On day 3, the hepatocytes were swollen with indistinct cell boundaries, and focal nuclei fragmentation was observed. Massive interstitial lymphocyte infiltration and partial loss of bile duct epithelium were also noted. On day 7, interstitial inflammatory cell infiltration regressed, hepatocyte degeneration was still evident, and bile duct epithelium was degenerated and lost. On day 21, the hepatocyte degeneration was not obvious, and the structure was clear. The bile duct epithelium was reactive and proliferated, and no significant interstitial inflammatory cell infiltration was observed.

In the PVA group, on day 1, the hepatocytes were swollen with fixed nuclei, the hepatic blood sinuses were dilated, and the bile duct epithelium mildly degenerated. On day 3, the hepatocytes were swollen with indistinct cell boundaries, and focal nuclei fragmentation was observed. Massive interstitial lymphocyte infiltration and partial loss of bile duct epithelium were also noted. On day 7, a large area of hepatocytes and bile duct epithelium was degenerated and necrotic, and the structure of liver lobules disappeared, replaced by infiltration of lamellar inflammatory cells. On day 21, the necrotic foci were further enlarged, and the surrounding hepatic blood sinusoids were infiltrated by lymphocytes (Fig. 2).

WB results. The Western Blot method was used to detect Bcl2 and Bax proteins in hepatocytes and biliary epithelial cells in liver tissues. Results showed that the expression of Bax protein in liver tissues increased on day 1, day 3, day 7, and day 21 in the PVA group, while in the AGS group, it showed an upward-downward trend and peaked on the third day. Bax apoptotic protein expression induced by PVA did not recover with time, while AGS-induced Bax apoptotic protein expression showed a trend of recovery at day 7. The expression of Bcl2 protein in liver tissues decreased on days 1, 3, 7, and 21 in the PVA group, and the expression in the AGS group decreased significantly on day 3 and showed an increasing trend after day 7. The expression of the anti-apoptotic protein was inhibited in the PVA group, with no recovery trend observed with time. Conversely, the expression of the anti-apoptotic protein was inhibited in the AGS group, but a recovery trend was evident with time at day 7. The Bcl2/Bax ratio can be used to measure apoptosis and repair of liver tissues. The Bcl2/Bax ratio serves as a measure of apoptosis and tissue repair in the liver. In the AGS group, the Bcl2/Bax values showed an upward trend on day 7 following a decline on days 1 and 3, while in the PVA group, the Bcl2/Bax values did not show a significant upward trend after declining from day 1. The Bcl2/Bax ratio in the AGS group was higher than that in the PVA group on both day 7 and day 21, and the difference was statistically significant (Fig. 3; Tables I and II).

Discussion

TAE is increasingly becoming the main therapeutic approach for traumatic hepatic rupture haemorrhage and is more frequent in the clinic, as a result of many clinical studies (14,15). TAE treatment involves the delivery of embolic material through the hepatic artery to the site of liver injury to stop bleeding or treat the lesion, and the effectiveness of the treatment is influenced by the skill level of the intervening physician, the level of the embolic artery and the property of the embolic material itself. The commonly used embolic materials can be divided into various types, and according to their ability to be absorbed in the body, they can be divided into absorbable and non-absorbable embolic materials. AGS and PVA are short- and medium-term and permanent embolic agents for large and medium vessels in the body that are widely used in clinical practice and have achieved certain results in treatment (16,17). However, there are still few studies related to whether there are differences in the pathological changes caused by local tissue ischemia in the liver after TAE treatment with different embolic materials, especially the structural and functional changes of the bile ducts after ischemia.

AGS has been clinically used for a long time, and a lot of experience has been accumulated in its use. AGS has the advantages of weak antigenicity, good histocompatibility, and biosafety (18,19). In addition to mechanical embolism, the sponge-like framework of gelatin sponge can be filled with red

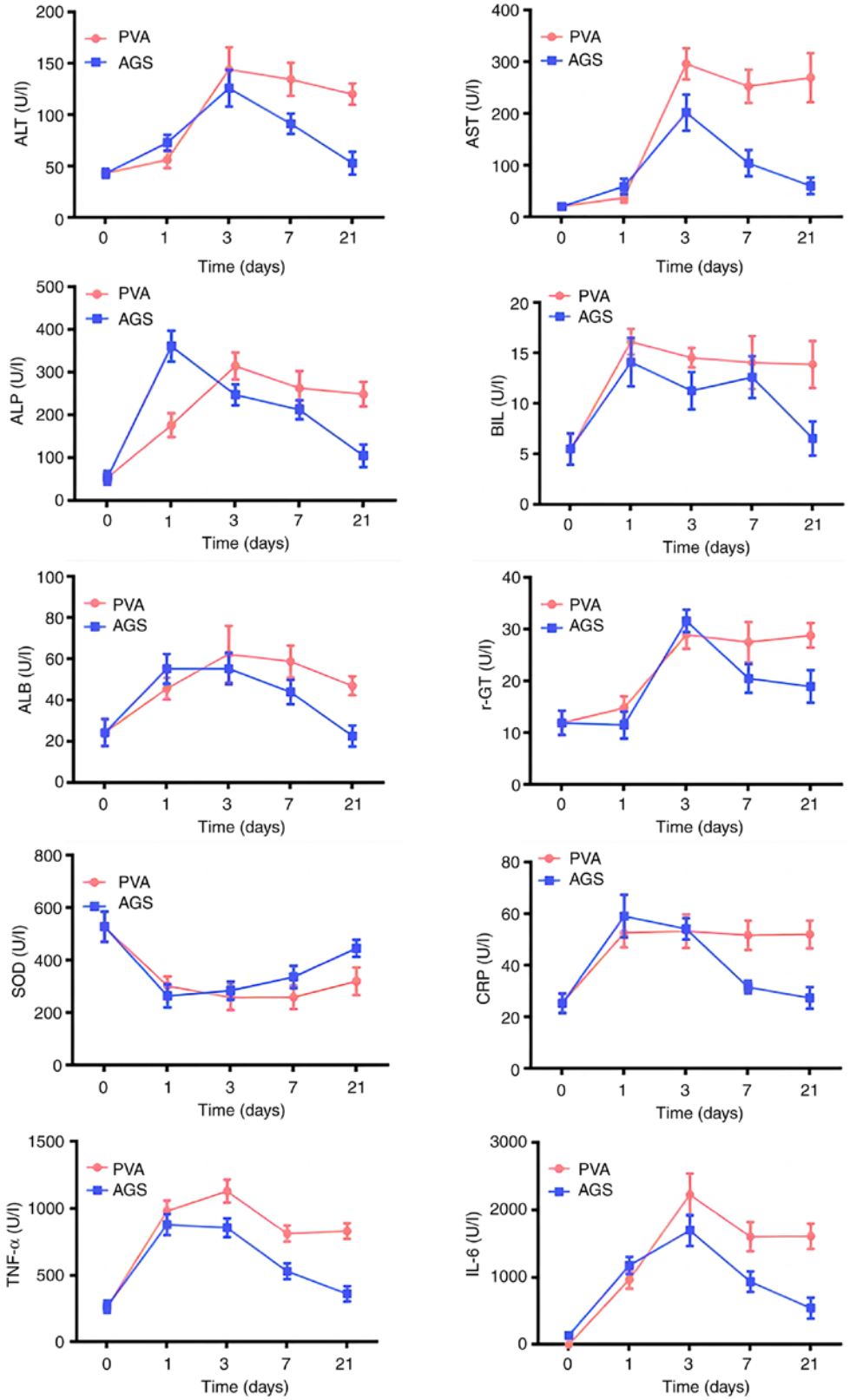

Figure 1. Changes of 10 indicators in the serum of the embolism model rabbits at five time points detected by ELISA. AGS, absorbable gelatin sponge; ALB, albumin; ALP, alkaline phosphatase; ALT, glutamate transaminase; AST, glutathione transaminase; BIL, bilirubin; PVA, polyvinyl alcohol particles; r-GT, r-glutamine transpeptidase; SOD, superoxide dismutase.

blood cells, which cause platelet agglutination and fibrinogen deposition in blood vessels, forming thrombus quickly, plus it causes vascular spasm also contribute to thrombus formation and help blood vessel embolism. Furthermore, during embolization, it can not only embolize the blood vessel to achieve the purpose of hemostasis but also the AGS can promote the growth of granulation tissue at the lesion site after adding chitosan to achieve the effect of promoting wound

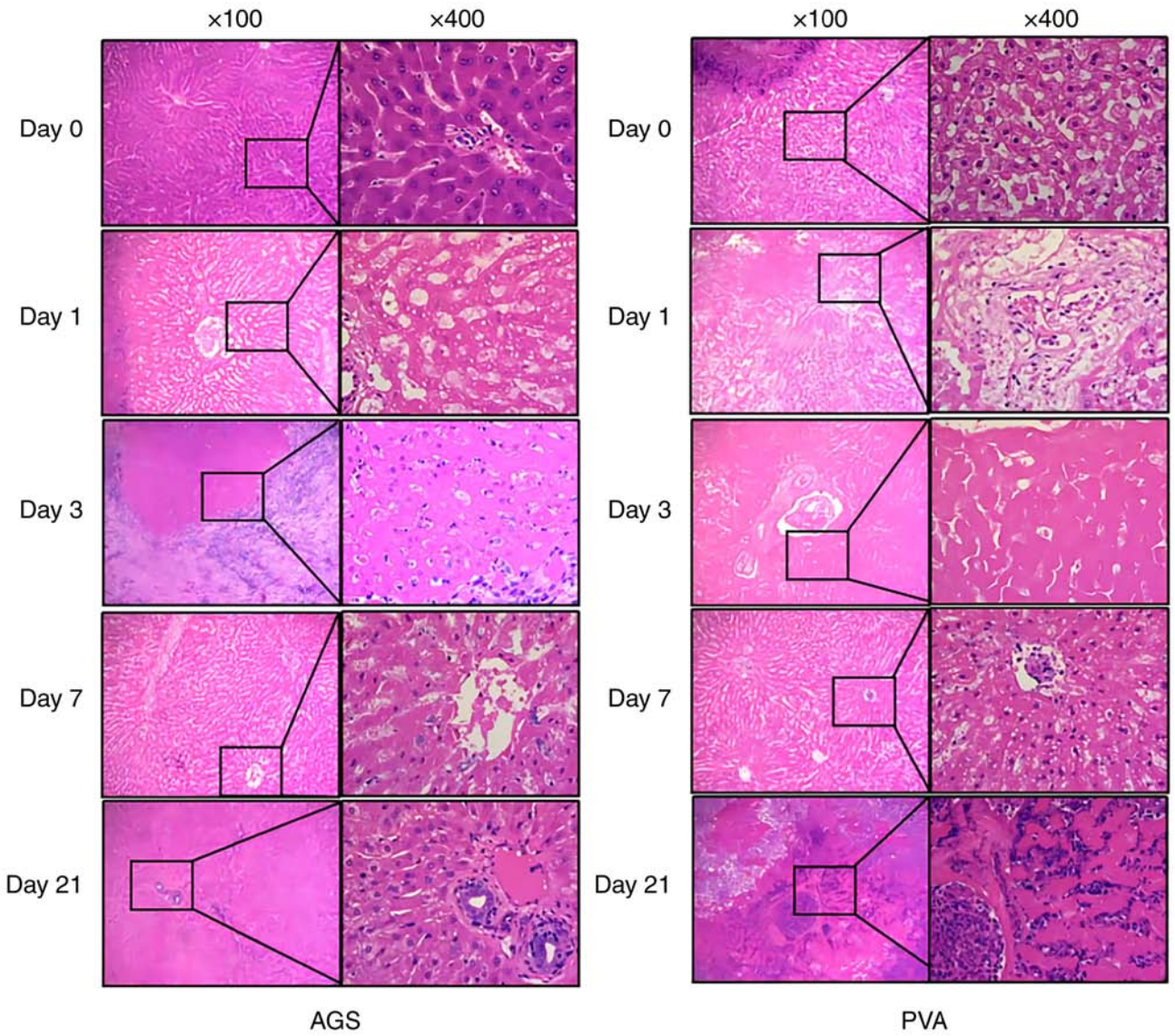

Figure 2. H&E staining to detect the structure of liver lobules-AGS and lobules-PVA. Magnification, x100 or x400. AGS, absorbable gelatin sponge; PVA, polyvinyl alcohol particles; H&E, hematoxylin and eosin.

recovery, which is suitable as the material of choice for hepatic artery embolization. AGS, as a non-permanent embolic material, usually takes a few weeks to a few months to be completely absorbed and degrades within a certain period of time after embolization to the designated site, resulting in the recanalization of the target vessel at the embolized site and thus failing to achieve the desired therapeutic effect or even the recurrence of serious bleeding. In the study, the liver function of the rabbits in the AGS group showed a trend of improvement at about one week after embolization, and all the indicators were statistically different until day 21 compared with those in the PVA group, and a better repair of hepatocytes and the biliary system was observed in HE. The WB results also showed that the Bcl-2/Bax ratio rebounded on days 7 and 21, showing inhibition of hepatocyte apoptosis and gradual repair of hepatocytes. As a permanent embolic agent, PVA can mechanically occlude the diseased vessels after being injected into the blood vessels, and thrombotic materials can form and become macerated in the gaps between the polyvinyl alcohol particles, leading to permanent vessel occlusion. In interventional embolization for liver trauma, compared with other embolic agents, PVA can provide a more long-lasting hemostatic effect because it cannot be degraded in the body, which also reduces the chance of vessel recanalization (20-22). de Baere *et al* (23) found a significant increase in liver fibrosis after embolization of the liver vessels with PVA compared to the control group in a pig experiment. The results of our study showed that the liver of the rabbits in the PVA group was more severely damaged than that of the AGS group, and there was no trend of recovery, and we could see that the necrosis of the hepatocytes and biliary system around the embolization was more severe under HE observation. This is also consistent with the fact that PVA is a permanent embolic material that cannot be recanalized after embolization. Therefore, this conventional embolic agent embolization of the hepatic artery has a therapeutic effect as well as serious liver damage caused by tissue ischemia after embolization of the liver.

Interventional embolization has been used in a large number of clinical studies and practical work, and the advantages of TAE over conventional open abdomen have been

Table I. Western-Blot detection of expression of proteins related to Bcl2 and Bax expression in the PVA and AGS groups at different time points.

A, Bcl2

	PVA			AGS		
Time, days	Sample 1	Sample 2	Sample 3	Sample 1	Sample 2	Sample 3
0	1.0945	1.1505	0.7550	0.8734	0.9375	1.1890
1	0.8153	0.9294	0.5126	0.7837	0.9605	1.0630
3	0.6867	0.7375	0.3982	0.4412	0.6223	0.4117
7[a]	0.4880	0.5876	0.4629	0.8021	0.7951	0.8742
21[a]	0.6708	0.6126	0.3935	0.8321	0.9635	1.1030

B, Bax

	PVA			AGS		
Time, days	Sample 1	Sample 2	Sample 3	Sample 1	Sample 2	Sample 3
0	0.8727	1.2881	0.8393	1.0243	0.8225	1.1532
1	1.3121	2.1829	1.3146	1.5102	1.3702	2.1276
3	1.1881	1.8128	1.1743	2.2644	2.0603	3.5177
7	1.1628	1.5789	1.1396	1.2588	1.1940	1.4549
21	1.0259	1.2590	1.1059	1.1599	1.1589	1.2658

[a]Bcl2/Bax ratio between the AGS and PVA groups (P<0.05). AGS, absorbable gelatin sponge; PVA, polyvinyl alcohol particles.

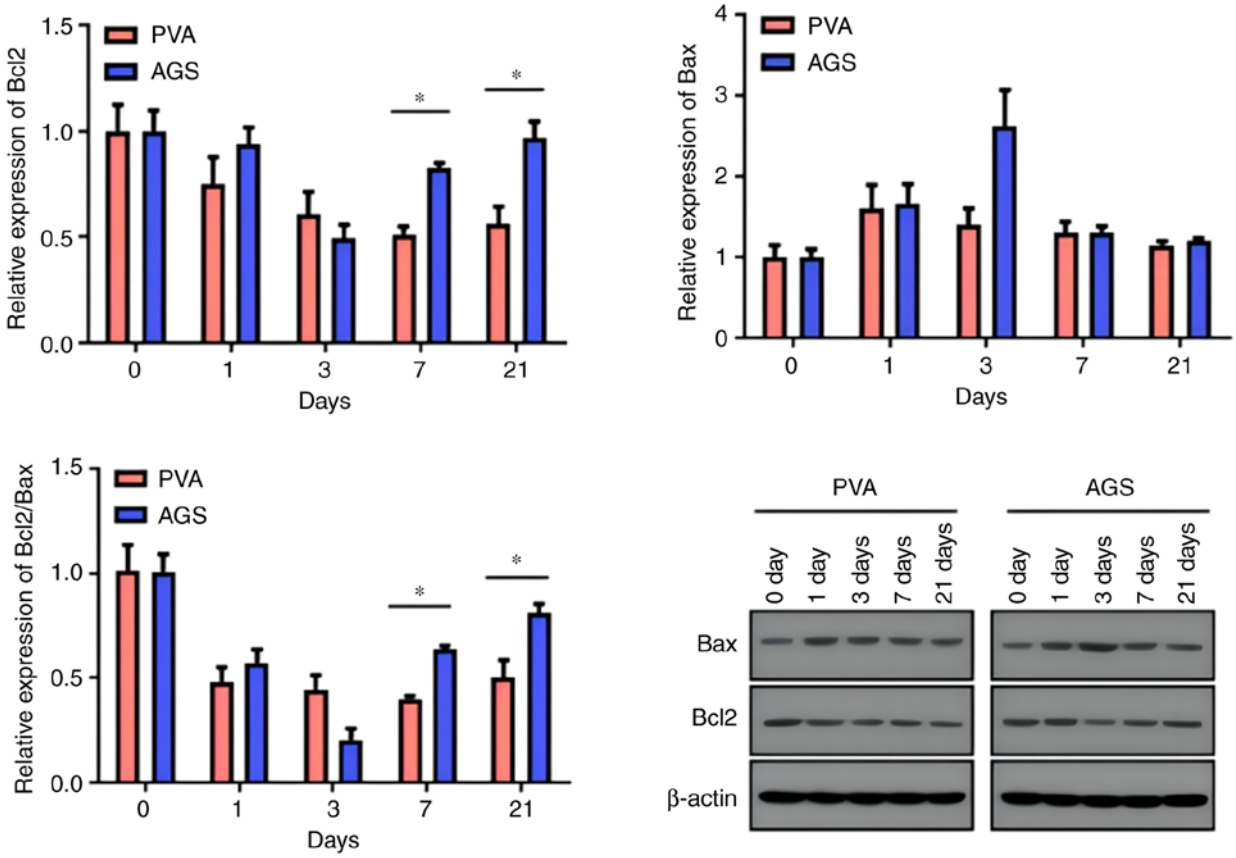

Figure 3. Bcl2 and Bax expression, as well as the Bcl2/Bax ratio in the AGS and PVA groups at different time points. *Indicates a statistically significant difference in the Bcl2/Bax ratio between the two groups. *P<0.05. AGS, absorbable gelatin sponge; PVA, polyvinyl alcohol particles.

Table II. Bcl2/Bax ratio in the PVA and AGS groups at different time points.

Time, days	PVA			AGS			t-value	P-value
0	1.2542	0.8932	0.8996	0.8527	1.1399	1.0311	0.0530	0.9600
1	0.6213	0.4258	0.3899	0.5190	0.7010	0.4996	-0.9770	0.3840
3	0.5779	0.4068	0.3391	0.1949	0.3020	0.1170	2.6580	0.0570
7[a]	0.4197	0.3722	0.4062	0.6372	0.6659	0.6009	-10.0020	0.0100
21[a]	0.6539	0.4866	0.3558	0.7174	0.8314	0.8714	-3.1490	0.0350

[a]Bcl2/Bax ratio between the AGS and PVA groups (P<0.05). AGS, absorbable gelatin sponge; PVA, polyvinyl alcohol particles.

studied, but the choice of embolization material is crucial in performing TAE treatment because of the different characteristics of various embolic materials and their application conditions (18). The liver is subject to the dual blood supply of the hepatic artery and portal vein, so it is rich in blood transport (24), and the liver has a better compensatory function after performing TAE, but for biliary epithelial cells, the blood supply to the porta hepatis or Hepatic portal vein and intrahepatic bile ducts depends only on the source of tiny branches of the hepatic artery, and the interventional treatment repeatedly embolizes these tiny arterial branches, thus may cause ischemic necrosis and fibrous tissue proliferation in the corresponding bile ducts, to the extent that some of the bile ducts are narrowed, while distal bile ducts are dilated due to biliary stasis, gallstone formation, and increased pressure in the bile ducts, thus causing more severe damage to the biliary system compared to the hepatocytes (25). A meta-analysis showed that the incidence of biliary fistula after performing TAE was about 5.7%, so we should be alert to the complications of the biliary system during TAE (26). In this study, it was found that the liver function of the AGS group compared to the PVA group in the 21-day control not only had better recovery of liver function, where the observation of HE and WB results also indicated that the function of their intrahepatic biliary epithelial cells in the AGS group also had some repair, and their biliary system complications The incidence of complications related to the biliary system was also relatively low. The use of permanent embolic agent PVA during TAE would have a better hemostatic effect due to the inability to revascularization, but at the same time, the damage to the liver and biliary tract would be more serious. In contrast, for AGS, the recanalized vessels can have a certain repair effect on the pre-ischemic liver and biliary tract, so the chance of related complications is lower, but it also undoubtedly increases the chance of bleeding after recanalization.

In conclusion, the current study has some limitations due to the small size of the New Zealand White rabbits, making it difficult to establish a standard model of liver trauma, and an embolization model based on liver trauma could not be established, therefore, we ultimately chose to establish an embolism model for the study. Future studies may need to consider using larger experimental animals to establish a liver trauma model and different embolic materials for validation to make the experimental results more representative of the real clinical situation.

In summary, this study investigated the effects of AGS and PVA on normal liver tissue by embolizing New Zealand rabbits and analyzed the differences in the effects of these two materials on normal liver tissue after embolization. The absorbable embolic material, gelatin sponge, caused less ischemic necrosis to the liver tissue after embolization than the non-absorbable embolic material, PVA, and the liver had some self-repair after revascularization. In contrast, PVA caused more damage to the liver tissue after embolization, and no obvious repair process was observed. Therefore, the choice of embolization material in clinical practice should be based on the patient's specific situation, and a more reasonable option should be chosen by balancing the therapeutic effect and possible complications after embolization.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SZ, JL and SW contributed to the conception and design, data collection, data analysis/statistics, data interpretation and funding collection. SW and JL contributed to the acquisition of data and preparation of the manuscript. XX, XP, TH and JH contributed to the analysis and interpretation of data. All authors have read and approved the final manuscript. SZ and JL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Animal Experimentation Committee of Xiamen University (approval no. XMULAC20230016; Zhangzhou, China), and all rabbits were handled in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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