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WORD COUNT	4348	TIME SUBMITTED	08-JAN-2024 09:08PM
		PAPER ID	106001228

Name of Journal: *World Journal of Gastrointestinal Surgery*
Manuscript NO: 88628
Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

Will preoperative partial splenic embolization followed by splenectomy lead to increased intraoperative bleeding? A nomogram-based prediction for a 6-year Single-Center Study

Splenic embolism increases bleeding risk

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Abstract

BACKGROUND

Partial splenic embolization(PSE) has been suggested as an alternative to splenectomy for treating hypersplenism. However, some patients may experience a recurrence of hypersplenism after PSE and still require splenectomy. Currently, there is a lack of evidence-based medical support regarding whether preoperative PSE followed by splenectomy reduces the incidence of complications.

AIM

The purpose of this study was to investigate the safety and therapeutic efficacy of preoperative PSE followed by splenectomy in patients with liver cirrhosis and hypersplenism.

METHODS

Between January 2010 and December 2021, a total of 321 consecutive cirrhotic patients with hypersplenism underwent splenectomy in our department. Based on whether PSE

was performed prior to splenectomy, patients were divided into two groups: PSE Group(n = 40) and Non-PSE Group(n = 281). The characteristics of the patients, postoperative complications, and follow-up data were compared. Propensity score matching(PSM) was conducted, and univariable and multivariable analyses were used to establish a nomogram predictive model for intraoperative bleeding(IB). The ROC curve, Hosmer-Lemeshow goodness-of-fit test, and decision curve analysis(DCA) were employed to evaluate the differentiation, calibration, and clinical performance of the model.

RESULTS

After PSM was conducted, the Non-PSE Group showed significant reductions in hospital stay, intraoperative blood loss, and operation time (all P=0.00). Multivariate analysis revealed that length of the spleen, portal vein diameter, splenic vein diameter, and PSE history were independent predictive factors for IB. A nomogram predictive model of IB was constructed, and DCA demonstrated the clinical utility of this model. Both groups exhibited similar results in terms of overall survival during the follow-up period.

CONCLUSION

Preoperative PSE followed by splenectomy may increase the incidence of IB, and the nomogram-based prediction model could predict the occurrence of IB.

Key Words: Partial splenic embolization; Splenectomy; Hypertension; Portal; Liver Cirrhosis; Intraoperative bleeding

Huang L, Li Q, Yu Q, Peng H, Zhen Z, Shen Y, Zhang Q. Will preoperative partial splenic embolization followed by splenectomy lead to increased intraoperative bleeding? A nomogram-based prediction for a 6-year Single-Center Study. *World J Gastrointest Surg* 2023; In press

Core Tip: Partial splenic embolizationn (PSE) has been suggested as an alternative to splenectomy for treating hypersplenism, but some patients may experience a recurrence of hypersplenism after PSE and still require splenectomy. Preoperative PSE followed by splenectomy may increase the incidence of intraoperative bleeding(IB), and the nomogram-based prediction model could predict the occurrence of IB.

INTRODUCTION

Cirrhosis, the end stage of different chronic liver injuries, is frequently accompanied by severe complications such as portal hypertension (PH), esophageal and gastric variceal bleeding (EGVB), splenomegaly, and hypersplenism [1, 2]. Previously, splenectomy has been used to treat patients with cirrhosis and hypersplenism [3]. Furthermore, a combined approach of splenectomy and periesophagogastric devascularization has shown to be an effective treatment option for cirrhotic patients with EGVB and PH. However, it is important to note that this procedure carries the risk of postoperative complications, including abdominal hemorrhage, pancreatic fistula, and portal vein thrombosis (PVT) [4]. Therefore, partial splenic embolization (PSE) has been proposed as an alternative method for managing hypersplenism instead of splenectomy [5].

Currently, PSE has emerged as a crucial treatment modality for hypersplenism associated with PH. It effectively treats hypersplenism, lowers portal pressure, and improves liver function[6,7]. The occurrence of acute ischemia of the splenic segment tissue and subsequent splenic infarction is attributed to PSE. The subsequent absorption of necrotic tissue and the development of splenic tissue fibrosis result in spleen atrophy and a reduction in spleen volume. The reduction in spleen volume enhances the space within the splenic pedicle, leading to a more precise disconnection between the perisplenic ligament and splenic pedicle vessels. As a result, this reduces the occurrence of complications[8]. Despite the therapeutic effectiveness of PSE in treating

hypersplenism and reducing PH, some patients may experience a recurrence of hypersplenism following PSE treatment, leading to the need for splenectomy[9].

Previous research has indicated that PSE reduces surgical complexity and lowers the occurrence of postoperative complications[10]. However, some studies suggest that PSE increases perisplenic adhesions and intraoperative bleeding (IB) during splenectomy[11]. Despite these findings, there is insufficient evidence-based medicine support to determine whether preoperative PSE followed by splenectomy reduces complications, and the optimal timing for performing splenectomy after PSE remains uncertain. Furthermore, there is limited research on predictive factors of complications for patients undergoing preoperative PSE followed by splenectomy.

The objective of this study was to assess the safety and therapeutic effectiveness of preoperative PSE followed by splenectomy in patients with liver cirrhosis and hypersplenism. Furthermore, the study aimed to examine the occurrence of complications. To achieve these objectives, a retrospective analysis of the clinical data of patients who underwent preoperative PSE followed by splenectomy in our hospital over a period of 6 years was conducted. The ultimate goal was to develop a reliable risk model that could identify independent risk factors for IB in individuals with cirrhosis.

MATERIALS AND METHODS

Prior to commencing this study, the objectives and specific details were comprehensively explained to the participants, and informed consent was obtained from each participant or their respective representatives. The investigation was conducted in adherence to The Code of Ethics of the World Medical Association (Declaration of Helsinki, revised in Fortaleza, Brazil, October 2013). The study protocol received approval from the Institutional Review Board (IRB) of Anhui Provincial Traditional Chinese Hospital (ID: 2020AH-13).

Patient selection and study design

From January 2017 to June 2023, a total of 344 consecutive patients underwent splenectomy at the First Hospital affiliated with Anhui University of Traditional

Chinese Medicine. After carefully applying inclusion and exclusion criteria, a total of 321 patients were enrolled in this study. The study employed a retrospective cohort design, where patients were divided into two groups based on whether they received preoperative PSE: the PSE group and the non-PSE group. Detailed assessments were conducted to evaluate the clinical characteristics of the included patients, including age, sex, etiology of cirrhosis, spleen size, and portal vein system diameter. Additionally, intraoperative outcomes such as blood loss and operation time, as well as postoperative complications like portal vein thrombosis (PVT) and postoperative pancreatic fistula (PPF), were collected and analyzed. Furthermore, the study reviewed the follow-up data on overall survival (OS) of the patients.

We meticulously collected and analyzed clinical data from a standardized database for patients during the perioperative period. Color Doppler ultrasound was utilized to measure the diameters of the portal and splenic veins, assess spleen size, and determine the presence of PVT.

All patients included in the study must meet the following inclusion criteria: (1) have a diagnosis of cirrhosis and PH of any etiology; (2) display secondary splenomegaly and hypersplenism attributed to cirrhosis. Hypersplenism is defined as a leukocyte count less than 3.5×10^9/L and a platelet count less than 7.5×10^9/L[12]; (3) have not previously undergone splenectomy.

The study excluded participants who had the following conditions: (1) those with liver cirrhosis without hypersplenism or splenomegaly; (2) those with severe coagulation dysfunction; (3) those with liver or any other malignancy; (4) those who declined to participate; and (5) those who underwent early postoperative transfer. All surgical procedures were non-emergency operations.

Partial splenic embolization and surgical technique

The puncture point for the right femoral artery was chosen at the most prominent point of the femoral artery pulse located under the inguinal ligament. The right femoral artery was punctured using the modified Seldinger technique under DSA guidance. The imaging results were used to superselectively advance the microcatheter into the

splenic artery. The extent of splenic artery embolism typically ranges from approximately 50% to 70%.

All patients enrolled in the study underwent endotracheal intubation and received intravenous anesthesia for open splenectomy. The splenic artery was fully exposed for ligation, and the serosal tissue in front of the splenic pedicle space was separated and dissected after the separation of perisplenic adhesions (Figure 1). To ensure a safe dissection, it should be performed as close as possible to the splenic parenchyma to avoid the pancreatic tail and stomach. Each secondary splenic pedicle vessel was carefully dissected and ligated under direct vision. After that, the splenic tissue was removed, ligated, and sutured. Finally, a drainage tube was routinely placed in the splenic fossa.

Postoperative complications

The study collected and analyzed data on postoperative complications following splenectomy during hospitalization. These complications included PVT, postoperative abdominal hemorrhage, abdominal infection, PPF, liver failure, severe ascites, and encephalopathy. The criteria for diagnosing PPF were as follows: 1) drainage duration exceeding 3 days, 2) amylase level in drainage fluid more than 3 times the upper limit of normal, and 3) no record of biochemical leakage [13]. PVT was defined as the presence of thrombosis in the portal vein (trunk and intrahepatic branches), mesenteric vein, or splenic vein, confirmed by Doppler ultrasound displaying hyperechoic or isoechoic filling in the cavity. Postoperative abdominal hemorrhage was defined as abdominal bleeding exceeding 300 mL within 24 h after surgery. Additionally, clinical details of the surgery, such as operation time, intraoperative blood loss, and hospital stay, were recorded.

Follow-up

All patients who underwent splenectomy received routine follow-up assessments, either *via* telephone or at the outpatient department. The follow-up assessment must be completed by June 30, 2023. The primary endpoint was overall survival (OS). OS was

defined as the duration from surgery until death from any cause. Patients who were alive at the last follow-up were considered censored.

Statistical analysis

The statistical analyses and plotting were conducted using SPSS Version 24.0 software (IBM Corp., Chicago, IL, USA) and R (Version 4.2.2). Continuous variables following a normal distribution were reported as mean ± standard deviation (mean ± SD). Non-normally distributed variables were reported as median with interquartile range (P25, P75). Group comparisons for measurement data were performed using independent t-test. Categorical variables were evaluated using χ^2 test with or without Fisher's exact test, as appropriate.

A propensity score matching (PSM) was performed in order to eliminate confounding variables associated with clinical characteristics between the two groups. The propensity score matching was performed using the 1:1 nearest-neighbor caliper matching method, with a caliper value set at 0.2 [14]. Intraoperative bleeding was assessed for its influencing factors using univariable analysis. Those variables that showed statistical significance (P<0.05) were further evaluated through multivariable logistic analysis to identify the main independent risk factors. A nomogram was constructed using R software (Version 4.2.2), and the differentiation of the nomogram was assessed by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. To evaluate the clinical utility of the nomogram model, decision curve analysis (DCA) was conducted using the R "rmda" package. Survival curves were plotted using the Kaplan-Meier method, and differences between the two groups were assessed using the log-rank test. Statistical significance was considered at the 5% level, with a 2-tailed test used for analysis.

RESULTS

Comparison between the two groups by PSM analysis

A total of 23 patients were excluded from the study out of the initial 344 patients who met the inclusion criteria. Among them, 8 patients had idiopathic thrombocytopenic

purpura (ITP), 4 patients had hereditary spherocytosis and underwent splenectomy, showing no symptoms of hypersplenism or splenomegaly, 4 patients developed severe coagulopathy, 3 patients had liver malignancy, and 4 patients experienced early postoperative complications. Ultimately, a total of 321 patients who met the inclusion criteria were enrolled in the study.

Among the 321 patients, there were 173 men and 148 women. The PSE group comprised 40 patients, while the non-PSE group included 281 patients (Figure 2).

When comparing the baseline clinical data between the PSE group and the non-PSE group, no significant differences were observed in various indicators, including age, sex, etiology of cirrhosis, and the diameters of the portal and splenic veins (all $P>0.05$). Additionally, no significant differences were observed in parameters including WBC, RBC, HGB, ALT, PT, and operation between the two groups (all $P>0.05$). In contrast to the PSE Group, the non-PSE Group demonstrated significantly reduced hospital stay (13.99 ± 3.57d *vs* 17.10 ± 4.42d), intraoperative blood loss (267.36 ± 161.07 mL *vs* 399.50 ± 240.76 mL), and operation time (181.64 ± 36.57min *vs* 202.98 ± 36.38min) (all $P=0.00$).

Table 1 presents the results of the Propensity Score Matching (PSM) conducted at a 1:1 ratio, resulting in 23 patients in each group. Following PSM, the clinical data of the matched PSE Group were found to be comparable to those of the matched non-PSE Group, with all P-values exceeding 0.05. Furthermore, the matched non-PSE Group demonstrated significantly reduced hospital stay (13.52 ± 2.25 days compared to 16.70 ± 4.18 days), intraoperative blood loss (250.13 ± 129.02 mL compared to 450.00 ± 268.40 mL), and operation time (178.78 ± 37.42 minutes compared to 220.09 ± 35.41 minutes) when compared to the matched PSE Group.

Comparison among pre- or post- PSE

Notable variations were observed in multiple indices between pre- and post-PSE, specifically in the diameters of the portal and splenic veins, along with changes in HGB, PLT, TBIL, ALT, AST, ALB, and PT levels (all $P<0.05$). No significant differences were observed in the spleen's length and thickness, as well as WBC, RBC, and D-dimer levels (all $P>0.05$) (Table 2).

Risk factors of intraoperative bleeding using the uni- and multi-variable analyses

IB was defined as a volume exceeding 300mL, determined by the median of the intraoperative bleeding volume. A total of 26 patients (56.5%) experienced IB during splenectomy. Univariable analysis revealed significant differences in various indicators, including ALB, PT, the length of the spleen (LS), the thickness of the spleen, portal vein diameter (PVD), and splenic vein diameter (SVD), and PSE history (all $P<0.05$), when assessing the predictive factors of IB. Multivariable logistic analysis further confirmed that LS, PVD and SVD, and PSE history were independent risk factors for predicting PVT (Table 3).

The construction of prediction model

Univariate and multivariate logistic regressions were employed to develop the clinical prediction model, with the occurrence of IB serving as the dependent variable and incorporating the four selected variables derived from LASSO regression analysis. The findings revealed that length of the spleen, PVD, SVD, and PSE history significantly influenced the occurrence of intraoperative bleeding ($P < 0.05$). A nomogram is depicted in Figure 3, which was constructed using the predicted variables.

The predictive performance of the differentiation model was assessed by generating a ROC curve and calculating the AUC to predict IB in the included patients following the procedure (Figure 4). The AUC results were 0.929 (95%CI: 0.950–0.846), indicating a strong discriminatory ability of the prediction model. Furthermore, the Hosmer-Lemeshow goodness-of-fit test ($P = 0.89$) demonstrated that the predicted probability of the model closely matched the actual probability, indicating a high degree of calibration. In summary, the nomogram models displayed superior predictive performance (Figure 5).

The DCA of the IB risk nomogram is illustrated in Figure 6. The results demonstrate that the net benefits are greater for threshold probabilities within the range of 20-99%, suggesting that intervention within this range is more favorable.

Follow-up

The follow-up rate in the non-PSE Group was 92.2% (259/281), and in the PSE Group it was 92.5% (37/40). The median follow-up time in the Control Group was 43 (29, 56) months, while in the Study Group it was 34 (15, 51) months. The log-rank test (P=0.62) indicated no significant differences in the follow-up data between the two groups (Figure 7).

In the non-PSE Group, there were a total of five deaths, whereas in the PSE Group, there was one death. Three patients in the non-PSE Group died due to liver failure during the follow-up period. One patient in the non-PSE Group developed refractory ascites and subsequently died from a spontaneous ascitic fluid infection. In both groups, one patient died from a pulmonary infection each.

DISCUSSION

With the advancement of interventional radiology, PSE has gained widespread use in clinical practice for the treatment of liver cirrhosis and hypersplenism. PSE is commonly used for patients with liver cirrhosis and hypersplenism who are in poor physical condition and unable to undergo surgical treatment, or as a preoperative treatment prior to splenectomy [15]. PSE has been demonstrated to reduce splenic volume, thereby improving surgical visibility and intraoperative exposure [16]. However, does preoperative PSE prior to splenectomy reduce surgical risks? Some institutions have performed preoperative PSE followed by splenectomy and arrived at conclusions that differ from ours [17-19].

PSE has the potential to reduce splenic venous blood flow, lower PH, and suppress splenic hyperfunction by impeding blood flow through the secondary splenic artery [20]. Furthermore, ischemic infarction may occur in the splenic region, and reducing splenic volume can be advantageous for splenectomy [21,22]. In contrast to previous studies, our research indicates that PSE followed by splenectomy may lead to increased perisplenic adhesions, prolonged surgical duration, and increased IB. We used PSM to control for confounding variables related to clinical characteristics between the two groups, and performed a logistic regression analysis to identify independent risk factors for IB. The

results of our study suggest that parameters such as LS, PVD, SVD, and a history of PSE significantly impact the occurrence of IB. Additionally, both the AUC and DCA indicated strong discriminative capabilities of the prediction model. The findings of this study suggest a potential increase in IB associated with preoperative PSE followed by splenectomy.

A comprehensive analysis of surgical procedures reveals that the disparity lies in the timing of preoperative PSE. According to the literature [23], conducting splenectomy within 24 h after PSE may reduce surgical risk. However, our findings indicate that performing splenectomy after a period exceeding 1 month following PSE increases surgical complexity and the likelihood of intraoperative bleeding.

Post-PSE complications can influence the therapeutic outcomes for patients. Complications include splenic infarction, splenic abscess, pleural effusion, spontaneous bacterial peritonitis, ectopic embolization, portal and splenic vein thrombosis, ascites, jaundice, and liver failure [24]. Splenic infarction is classified into four stages: hyperacute, acute, subacute, and chronic [25]. The first stage lasts approximately one day, during which the spleen tissue exhibits congestion and edema. The second stage lasts around one week and is characterized by inflammatory exudation in the spleen tissue and the formation of mild perisplenic adhesions. The third stage lasts from one week to one month and is characterized by a reduction in inflammation in the spleen tissue, leading to the development of dense adhesions with surrounding tissues like the omentum. The fourth stage lasts for over a month and is characterized by fibrosis and scar formation in the spleen tissue [26]. Therefore, if splenectomy is performed more than a month after PSE, dense adhesions around the spleen can result in IB. However, only a small number of patients undergo splenectomy within a day after PSE, and the purpose of PSE sequential splenectomy is to reduce intraoperative splenic volume and facilitate surgery. Therefore, for most patients, the timing of splenectomy surgery is more than a month after PSE[27].

Unlike previous literature [28], our splenectomy is typically performed one month or more after PSE, which may contribute to increased IB. Enlarged spleens can limit

surgical space and exposure, increasing surgical risk. PSE can reduce the size of the spleen, enhance operating space, and facilitate exposure. PSE can mitigate PH, improve liver function, and alleviate hypersplenism symptoms, making it a potential alternative to splenectomy. Preoperative PSE before laparoscopic splenectomy can reduce surgical complexity and postoperative complication rates [29, 30]. Some suggest that PSE patients are at risk of intraoperative massive bleeding due to splenic infarction, extensive adhesions, and thickened collateral circulation vessels. PSE patients who undergo splenectomy may experience prolonged operation times, substantial bleeding, and postoperative complications due to blood protein and coagulation factor loss. They also have longer hospital stays compared to those without PSE. Currently, there is no consensus on the preferred embolization plan or the optimal timing for splenectomy after embolization.

The optimal duration between embolization and splenectomy requires further investigation. It has been established that a duration of PSE and splenectomy less than 24 h effectively reduces splenic volume, enhancing surgical visibility and exposure, thereby decreasing the risk of surgical complications. However, this study only considered cases with a duration exceeding one month. The results suggest that while a duration exceeding one month may increase the risk of splenic adhesions-related complications, it can also improve liver function and facilitate surgical exposure by reducing an enlarged spleen.

The study focused on PSE cases with an embolization duration exceeding one month. A significant reduction in spleen size was observed through a comparison of color Doppler ultrasound images before and after embolization. However, during the intraoperative exploration, it was observed that there was extensive inflammatory exudation and adhesion around the spleen, which resulted in a significant increase in IB and prolonged hospital stay. Therefore, based on the findings of this study, it is necessary to adopt precise intraoperative procedures and carefully separate adhesions for patients with an embolization duration exceeding one month to minimize IB.

Moreover, LS, PVD, and SVD were significant factors that contributed to IB. The elongated shape of the spleen can result in adhesion between its upper end and the stomach, which can further complicate the dissection of the short gastric artery and lead to increased surgical complexity and IB. Similarly, an increase in the diameter of the portal vein and splenic vein can lead to tortuous dilation of vessels within the splenic pedicle, making separation more challenging. Consequently, detaching the splenic pedicle can lead to an increase in IB. This suggests that further investigation and research are needed to evaluate the long-term efficacy of PSE as a treatment for cirrhotic patients with PH and hypersplenism.

Nomograms, which are graphically intuitive representations in mathematical models, have the ability to predict specific end points by integrating multiple influencing factors. This is due to their ability to provide personalized assessments, thereby facilitating disease management and clinical decision-making[31]. Our study examined the clinical characteristics, hematology, and complications of patients diagnosed with cirrhosis and PH. Through the use of LASSO, univariate, and multivariate regression analyses, we identified several influencing factors of IB, including LS, PVD, SVD, and PSE history. To facilitate visual analysis of complications, we developed a nomogram. We identified four influencing factors of IB in this study. Subsequently, we internally and externally validated the established model. The AUC was 0.929 (95%CI: 0.950–0.846), indicating the robustness of the model as revealed by the Hosmer–Lemeshow goodness-of-fit test (P = 0.89). Furthermore, the DCA plot indicates a favorable clinical net benefit of the nomogram.

In this study, several limitations should be addressed. Firstly, the retrospective nature of the study and its focus on a single institution limit the generalizability of the findings. Additionally, a small proportion of discharged patients were lost to follow-up, and the sample size of patients with preoperative PSE was also limited. To draw more comprehensive conclusions, a prospective randomized multicenter study is recommended. Furthermore, it is crucial to investigate the molecular mechanism of

perisplenic adhesions after PSE through animal and cell experiments, as this remains an area of uncertainty.

CONCLUSION

In summary, preoperative PSE followed by splenectomy may lead to an increased incidence of IB in cases of severe splenic adhesions. This results in significantly prolonged surgery duration and heightened surgical risk. Additionally, the nomogram-based prediction model effectively predicts the occurrence of IB.

ARTICLE HIGHLIGHTS

Research background

Partial splenic embolization(PSE) has been suggested as an alternative to splenectomy for treating hypersplenism, but some patients may experience a recurrence of hypersplenism after PSE and still require splenectomy. Research has demonstrated that PSE can diminish the surgical complexity and lower the occurrence of postoperative complications. Currently, there is a lack of evidence-based medical support regarding whether preoperative PSE followed by splenectomy reduces the incidence of complications.

Research motivation

There is a lack of clear evidence-based medicine support regarding whether preoperative PSE followed by splenectomy can decrease complications and the optimal timing for performing splenectomy after PSE remains uncertain. Addressing these questions is crucial to providing evidence-based guidance for clinicians to decrease perioperative complications.

Research objectives

The purpose of this study was to investigate the safety and therapeutic efficacy of preoperative PSE followed by splenectomy in patients with liver cirrhosis and hypersplenism.

Research methods

Between January 2010 and December 2021, a total of 321 consecutive cirrhotic patients with hypersplenism who underwent splenectomy were enrolled in this study. Based on whether PSE was performed prior to splenectomy, patients were divided into two groups: PSE Group(n = 40) and Non-PSE Group(n = 281). The characteristics of the patients, postoperative complications, and follow-up data were compared. Propensity score matching(PSM) was conducted, and univariable and multivariable analyses were used to establish a nomogram predictive model for intraoperative bleeding(IB). The ROC curve, Hosmer-Lemeshow goodness-of-fit test, and decision curve analysis(DCA) were employed to evaluate the differentiation, calibration, and clinical performance of the model.

Research results

After PSM was conducted, the Non-PSE Group showed significant reductions in hospital stay, intraoperative blood loss, and operation time (all P=0.00). Multivariate analysis revealed that length of the spleen, portal vein diameter, splenic vein diameter, and PSE history were independent predictive factors for IB. A nomogram predictive model of IB was constructed, and DCA demonstrated the clinical utility of this model. Both groups exhibited similar results in terms of overall survival during the follow-up period.

Research conclusions

Preoperative PSE followed by splenectomy may increase the incidence of IB, and the nomogram-based prediction model could predict the occurrence of IB. Meticulous

separation of splenic adhesions are imperative to attain safe and efficacious surgical outcomes.

Research perspectives

Future research should focus on the duration between embolization and splenectomy, which would enhance the benefits of this approach and reduce the surgical risks. Additional prospective, randomized controlled trials are necessary to expand upon the findings of this study.

ACKNOWLEDGEMENTS

We would like to acknowledge the support of the Department of No. 1 Surgery, the First Affiliated Hospital of Anhui Chinese Medical University, Hefei, China. The work was funded by the National Natural Science Foundations of China (no.8217141089) and Anhui Natural Science Foundation (no.2008085QH389).

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