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Clinical application of kelp micro gelation (KMG) in partial splenic embolization

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Abstract. – OBJECTIVE: We aimed to compare and analyze the long-term efficacy and safety between kelp micro gelation (KMG) and gelfoam particles in partial splenic embolization (PSE).

PATIENTS AND METHODS: This study retrospectively included 65 liver cirrhosis patients with comorbidity of hypersplenism who were admitted in Nanfang Hospital from July 2008 to May 2012. Among the included patients, 33 patients were in KMG-PSE group, and 32 cases were included in Gelfoam-PSE group. According to the Child-Pugh criteria, all cases were divided into grade A, B, and C, respectively. All eligible subjects received CT or MR examination and laboratory examination.

RESULTS: Our results showed that both KMG and gelfoam particles could substantially improve the short-term efficacy of thrombocytopenia leukopenia. However, the efficacy of KMG is superior to that of gelfoam. Due to the characteristic of KMG as a permanent agent, KMG may result in an obvious pain in the spleen after PSE, especially in patients with megalosplenia. KMG was more expensive than gelfoam particles. The complication rate in patents with great embolization was much higher than that with less embolization.

CONCLUSIONS: The efficacy of KMG is superior to that of gelfoam in both short-term and long-term. To effectively control the occurrence of severe complication, the embolization should be controlled less than 70% regardless of the embolization agents.

Key Words:
Kelp micro gelation, Gelfoam particles, Partial splenic embolization.

Introduction

Hypersplenism is a common complication of liver cirrhosis with decompensated portal hypertension. The traditional splenectomy has great trauma, multiple complications and high mortality in the perioperative period. Partial splenic embolization (PSE) is characterized by small operation area, less complications and the ability to keep part of the spleen function in comparison to traditional splenectomy. Therefore, it has been widely applied to treat leukopenia and thrombocytopenia induced by hypersplenism[1,2]. The main materials for embolism in traditional PSE include gelfoam particles[3-5] and stainless steel coil[6], in which gelfoam particles is more common due to its low cost and high availability. Clinical data[1,3,4] showed that splenic embolization can substantially improve peripheral hemogram, thus ameliorating the hypersplenism in early stage. Nevertheless, the long-term efficacy was less satisfactory. The current study was conducted to compare the efficacy of gelfoam particles and permanent histocompatible kelp micro gelation (KMG) (OD of 350-560 μm) A. In comparison to gelfoam particles, KMG has an easy access to spleen sinusoid and a long degradation time *in vivo*. Theoretically speaking, KMG shall achieve a better efficacy than gelfoam particles due to excellent embolization ability. However, there is little research on the application of KMG in PSE. In addition, the literature comparing the long-term efficacy between KMG and gelfoam particles is even less. In this work, we aimed to compare and analyze the long-term efficacy and safety between KMG and gelfoam particles in PSE.

Patients and Methods

Patients

We retrospectively included 65 liver cirrhosis patients with comorbidity of hypersplenism who were

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admitted in Nanfang Hospital from July 2008 to May 2012. There were 47 male and 18 female with an average age of 51.43 years (ranging from 19 to 80 years). Among the included patients, 33 patients (25 males and 8 females) were in KMG-PSE group, with an average age of 51.06 years (ranging from 19 to 80 years). 32 cases (22 males and 10 females) were included in Gelfoam-PSE group, with an average age of 51.88 ± 9.84 years (ranging from 29 to 74 years). According to Child-Pugh criteria, there are 24 cases in grade A, 32 cases in grade B and 9 cases in grade C. All eligible patients received CT or MR examination/laboratory examination and were diagnosed with liver cirrhosis complicated with hypersplenism. No significant difference was observed in age, sex, liver function grade, preoperational peripheral blood cell numbers and embolization degree between the two groups (all $p>0.05$), implying that the patients in the two groups were comparable. Baseline characteristics of patients were shown in Table I. This investigation was approved by the Ethics Committee of Nanfang Hospital. Signed written informed consent was obtained from all participants before the study.

Inclusion and Exclusion Criteria

The inclusion criteria are as follows: liver cirrhosis, spleen enlargement, with comorbidities of thrombocytopenia and leukopenia, white blood cell (WBC) $\leq 60 \times 10^9$/L and/or WBC $\leq 3 \times 10^9$/L. The exclusion criteria include: (1) patients with severe infection, septicopyemia, or with comorbidities of spontaneous peritonitis which may result in splenic abscess; (2) prothrombin time shorter than 70% of that in normal people; (3) patients with megalosplenia, severe jaundice or seroperitoneum and (4) patients had other advanced diseases. Patients meeting above criteria were included in the study and grouped in to KMG-PSE group and Gelfoam-PSE group according to their embolization materials.

Process of PSE

All processes were conducted in aseptic condition and all patients were subjected to local anesthesia. The operations were as follows: 5F sheath were inserted through femoral artery puncture. Under the guidance of guide wire, the catheter was led to the coeliac trunk artery for radiography. After the opening of the splenic artery was determined, the super selective catheter was inserted, through which the micro-catheter and supper selective catheter were led to the arterial branches of intermediate and lower part of the spleen, avoiding any other possible blood supply branches. Gelfoam particles (50-500 μm) or KMG (300-500 μm) pre-soaked in solution of gentamicin (80,000 u) with normal saline was used for embolization of spleen under monitoring. During the embolization, polysomnography was conducted to assess the embolization degree till the embolization reached 40-70% of the whole spleen. For patients with bigger spleen, the embolization may slightly be decreased (30-40%). The embolization was assessed by operator and experience DSA technicians (Figures 1 and 2). The final embolization was determined by CT after 2 weeks of PSE. The post-operational treatment included analgesia and temperature cooling.

Follow-up

All patients were not allowed to discharge from hospital until the complications of embolization and severe post-operational complications were disappeared. After patients were discharged, follow-up was conducted by Outpatient Department. The routine examinations for peripheral blood include items for WBC, blood platelet (PLT) and red blood cell (RBC). Patients were examined before operation, and at 7 d, 15 d and 1 month after operation; thereafter, once every three months till the 3rd year. The complications during follow-up were checked and recorded. All patients were subjected to CT or MR 2 weeks after PSE to reassess the embolization, by comparing with the preoperational CT images. The embolization was determined by calculation by working station. Every six months after operation, patients are required for CT/MR examination.

Statistical Analysis

The comparisons between two groups were conducted using *t*-test or χ^2-test. The comparisons between preoperational and post-operational parameters were analyzed using pairwise *t*-test. Data were processed using Statistical Product and Service Solutions 18.0 software (SPSS Inc., Chicago, IL, USA). $p<0.05$ was considered as statistically significant.

Results

Long-term Follow-up

A total of 65 patients successfully received PSE. The foam used in patients in Gelfoam-PSE group was 2 cm×6 cm and the particle used in patients in KMG group was ≤ 1.0 g KMG (half bottle). Du-

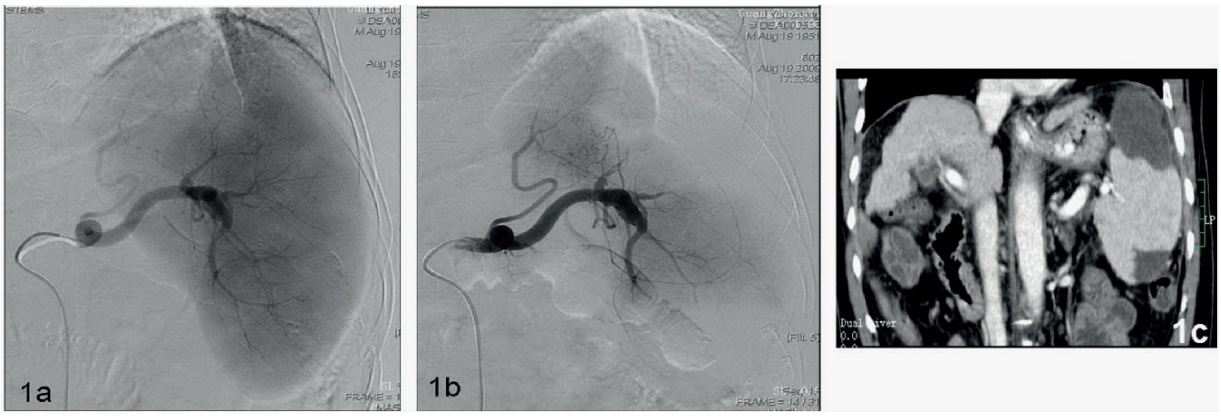

Figure 1. ***(A)*** Radiography before embolization indicating enlarged spleen parenchyma area. ***(B)*** Gelfoam-PSE group shows uneven dyeing and partial missing of the dyeing. ***(C)*** Reexamination after 2 W shows the infarcted area of lower and upper parts of the spleen reaching 55%.

ring the follow-up, 5 cases died from liver cancer within 2 years after PSE, 2 cases received surgical resection due to constant pain in spleen, and 2 cases were lost in follow-up. The rest of the patients were followed up till the 3rd year after operation.

Comparisons of Preoperational Peripheral Blood Cell Numbers Before and After Operation

Comparisons of preoperational peripheral blood cell numbers before and after operation were shown in Table II and III. No significant differences were observed in WBC and PLT between the two groups ($p>0.05$). The WBC and PLT measured on 2 weeks after operation and 3 years after operation were substantially higher than those measured before operation ($p<0.001$). The WBC and PLT measured on different follow-up time points in KMG group were significant higher than those in Gelfoam-PSE group ($p<0.05$).

Comparisons of Common Complications After Spleen Embolization

The most common complications after spleen embolization include pain, fever, nausea and vomiting (Table IV). The complications occurred between both groups had no significant difference (all $p>0.05$).

Comparisons of Severe Complications Between Two Groups After Spleen Embolization

5 cases of severe complication were reported in KMG group (15.2%) and 7 cases were identified in Gelfoam-PSE group (21.9%) after PSE for 1 month, among which 2 patients received paracentesis and

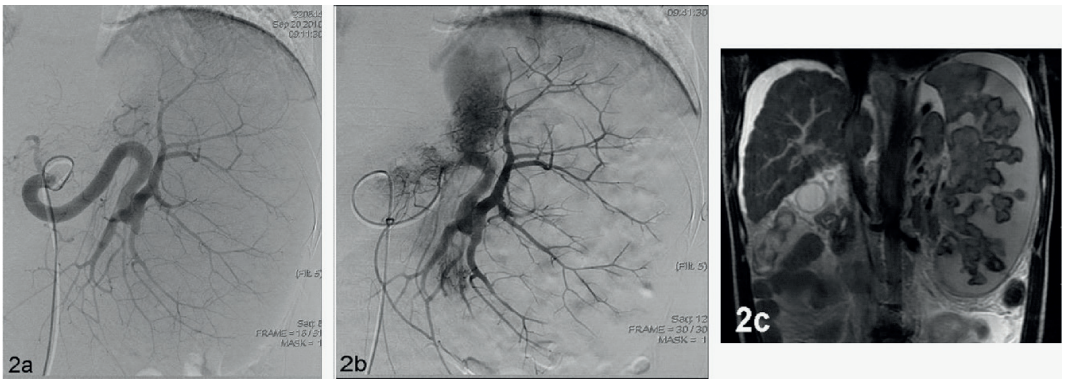

Figure 2. ***(A)*** Radiography before embolization indicating thickening and circuitous of splenic arteries and enlarged spleen parenchyma area. ***(B)*** KMG-PSE group shows partial missing of the dyeing in spleen peripheral area, in snow-flake shape. ***(C)*** Reexamination after 2W shows the infarcted area of spleen and spleen peripheral area reaching 75%.

Table I. Baselinecharacteristics of patients.

Groups	Statistical analysis KMG-PSE	Gelfoam-PSE	*X^2/*t*	*p*	Statistically
No.	33	32			
Sex (male/female)	25/8	22/10	0.398	0.528	NS
Average age					
Age ± SD (years)	51.06±12.882	51.88±9.843	-0.286	0.776	NS
Etiology (n)					NS
HBV (+)	30	30	0.185	0.667	
HCV (_)	3	2			
Others	0	0			
Child-Pugh criteria: A/B/C (n)	13/ 16 / 4	11/16 /5	0.262	0.877	NS
Embolization degree (%)					
$\bar{x}$±s	57.09±14.445	57.00±12.250	0.027	0.978	NS
Embolization range					
<50%	8	7	0.051	0.975	
50-70%	17	17			NS
>70%	8	8			

Enumeration data were compared using X^2-test or Fisher exact test, measurement data were analyzed using independent *t*-test, rank sum test was applied for ranked data, NS = not significant.

protein supplementation due to pleural effusion, peritoneum effusion, dyspnea, abdominal distension and abdominal pain; 3 patients received additional therapy due to bacterial peritonitis; 1 patient died from gastrointestinal bleeding (esophaheal variceal bleeding); 2 patients had constant high fever (> 38.5°C) and were confirmed as splenic abscess using blood cultivation and CT scanning (1 received paracentesis and recovered and 1 received surgical resection); 3 patients had portal venous thrombosis, while no additional therapy was conducted (thrombosis was dissolved in 2 cases during follow up) (Table V).

Complication on Embolization and Complication

Among the 12 patients who had severe complication, the embolization in 10 patients was greater than 70%, and the rest had embolization less than 70%. Among the 47 patients who had embolization less than 70%, severe complications were found in 2 cases 1 month after operation (3.7%); among the 16 patients who had embolization greater than 70%, severe complications were found in 10 cases 1 month after operation (62.5%). Using the embolization of 70% as cut-off value, patients were grouped into large embolization area (>70%) and small embolization area (≤70%). The complications were indicated in Table V. Patients with large embolization area had a significantly higher complication rate (p<0.001).

Discussion

PSE has been the optimal strategy to decrease portal venous pressure and to improve hyper-

Table II. Follow-up results of WBC counts (×109/L).

	KMG group (n = 33)				Gelfoam-PSE group (n = 33)				t*	*p*
	No.	$\bar{x}$ ± *s*	t*	*p*	N	$\bar{x}$ ± *s*	t*	*p*		
Before operation		2.62 ± 0.59				2.56 ± 0.46			0.425	0.673
After operation										
2 weeks	33	7.97 ± 2.28	12.293	<0.001	32	6.78 ± 2.48	9.721	<0.001	2.019	0.048
4 weeks	32	6.25 ± 1.47	11.668	<0.001	32	5.50 ± 1.03	15.366	<0.001	2.379	0.020
6 months	31	5.47 ± 1.25	8.297	<0.001	31	4.84 ± 0.98	12.294	<0.001	2.208	0.031
1 year	28	5.14 ± 1.13	12.083	<0.001	29	4.57 ± 0.74	14.201	<0.001	2.293	0.026
2 year	27	4.79 ± 0.70	13.277	<0.001	29	4.23 ± 1.07	9.653	<0.001	2.299	0.025
3 year	25	4.20 ± 0.83	8.746	<0.001	27	3.47 ± 0.50	7.818	<0.001	3.847	0.001

Note: *t** refers to comparisons on WBC counts with WBC before operation at different time points; *t** refers to comparisons on WBC counts on the same group at the same time points; WBC, white blood cell.

Table III. Follow-up results of PLT counts ($\times 10^9$/L).

	KMG group (n = 33)				Gelfoam-PSE group (n = 33)				t*	p
	No.	$\bar{x} \pm s$	t*	p	N	$\bar{x} \pm s$	t*	p		
Before operation		52.36 ± 10.71				52.25 ± 12.34			0.040	0.968
After operation										
2 weeks	33	143.39 ± 34.64	17.296	<0.001	32	124.28 ± 36.32	13.648	<0.001	2.171	0.034
4 weeks	32	119.00 ± 23.26	18.694	<0.001	32	104.94 ± 24.36	17.429	<0.001	2.362	0.021
6 months	31	105.23 ± 24.31	13.457	<0.001	31	92.97 ± 21.73	14.991	<0.001	2.093	0.041
1 year	28	99.86 ± 17.90	14.447	<0.001	29	89.01 ± 22.16	13.421	<0.001	2.209	0.047
2 year	27	92.74 ± 15.47	11.877	<0.001	29	78.59 ± 26.20	6.483	<0.001	2.438	0.018
3 year	25	94.50 ± 31.83	5.430	<0.001	27	75.04 ± 20.17	6.048	<0.001	2.638	0.011

Note: *t** refers to comparisons on WBC counts with WBC before operation at different time points; *t** refers to comparisons on WBC counts on the same group at the same time points; PLT, blood platelet.

Table IV. Comparison of embolization complication after spleen embolization between two groups.

Adverse reaction	No.	KMG-PSE (n = 33)				No.	Gelfoam-PSE group (n = 32)			
		0	I	II	III		0	I	II	III
		0	I	II	III		0	I	II	III
Pain		3	20	7	3		2	19	9	2
Fever		3	13	14	3		5	13	12	2
Nausea and vomiting	18	9	6	0	17		8	7	0	

Table V. Severe complications after PSE.

Complication	Embolization material		Embolization area	
	Gelfoam - PSE (n = 30)	KMG – PSE (n = 30)	>70% (n = 16)	≤70% (n = 47)
Pleural and peritoneum effusion	1	1	2	0
Bacterial peritonitis	1	2	2	1
Splenic abscess	2	0	2	0
Gastrointestinal bleeding	1	0	1	0
Portal venous thrombosis	1	2	2	1
PSE related death	1	0	1	0
Constant splenic pain	1	0	1	0
Total	7 (21.2%)	5 (16.7%)	10 (62.5%)	2 (4.3%)

splenism, replacing surgical spleen resection[1,3,4]. Among the embolization agents used in PSE, including stainless steel coil, gelfoam particles and PVA, gelfoam particles have been the most common used due to their high availability, low cost and relatively satisfying short-term efficacy. However, the long-term efficacy of gelfoam was less satisfactory[7]. This is possibly caused by the large size of gelfoam particles, which may lead to embolization of splenic artery braches and consequently result in severe complication and uncomplete spleen necrosis[8]. In comparison, sodium alginate (the material for KMG) has the following advantages as an embolization material: (1) biological material with good biocompatibility; (2) compared with PVA, it has satisfactory biodegradability, which can be degraded into polysaccharide, mannose and glucose after 3 to 6 months. In addition, it has no side-effect to human body, as it is non-toxic and can be discharged with the urine; (3) it can be specially made so as to adjust embolization requirements and can be enlarged in blood for accurate insertion in target vessels. Gelfoam particles cause vascular embolization predominantly due to mechanical embolization and the promotion of thrombus formation. The

time of occlusion of the targeting blood vessels ranges from a few days to a few months. However, recanalization may occur if the amount of Gelfoam used is not enough or the occlusion is not enough strong, thereby resulting in recurrence in the short- and medium-term of embolic cases. In comparison, when KMG is dissolved in water, it can form a viscous colloid and produce macromolecular cross-linking, and become solidity. This is the mechanism of its permanent embolic effect. Besides, this long-term stability also effectively reduces the possibility of absorption in the diseased vascular in the early and medium-term stages. Currently, there are a few studies reporting the application of KMG in PSE. Therefore, we aimed to compare the long-term efficacy of KMG and gelfoam particles on spleen embolization and to detect whether KMG was able to improve WBC and PLT in patients who undergone PSE. Our data showed that both KMG and gelfoam particles could substantially improve thrombocytopenia leukopenia in short-term. However, the effects of KMG are superior to that of gelfoam group in short- and long-term. We verified the safety of KMG in hypersplenism and found no significant difference between gelfoam particles and KMG groups. The severe complications after PSE were reported in other studies. Sakai et al[9] showed among the 17 liver cirrhosis patients with hypersplenism and received PSE using gelfoam particles, 2 patients had severe complications, one of which died due to the deterioration of liver function and liver failure. Vujic et al[10] reported 3 deaths due to liver failure, pneumonia, septicopyemia and abscess after PSE using gelfoam particles for 6 weeks. Other studies[11,12] using gelfoam particles also reported severe complications such as pleural and peritoneum effusion, spleen rupture and portal venous thrombosis. In above researches, the patients with grade C liver function and great embolization degree had a significantly higher risk of severe complications. Our study also identified that patients with embolization greater than 70% suffered more post-operational complications. In this regard, the embolization should be controlled under 70% regardless of the embolization agents.

Conclusions

KMG can be used as a safe and effective embolization agent in PSE. It has superior effects compared to gelfoam particles in PSE in both short-term and long-term. The embolization area should be controlled within 70%.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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