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Original Article

Spray of peppermint oil on papilla shortens the cannulation time of endoscopic retrograde cholangiopancreatography (ERCP): a randomized study

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Abstract: *Objective:* Endoscopic retrograde cholangiopancreatography (ERCP) is widely used for the diagnosis and treatment of pancreatobiliary disease but requires a high level of endoscopic techniques, especially cannulation of the common bile duct (CBD). Peppermint oil has been reported to inhibit the contraction of smooth muscle. We hypothesized that spray of peppermint oil on papilla can shorten the cannulation time of ERCP. *Methods:* 160 patients suspected of pancreatobiliary disease were randomly assigned to Peppermint oil group (group PO, n = 80) and Normal saline group (group NS, n = 80). After insertion of the duodenoscope and find the duodenal papilla, 20 mL of 1.6% peppermint oil solution (group PO) or Normal saline (group NS) was sprayed on the papilla by syringe via the working channel. The Deep CBD cannulation time, success rate of biliary cannulation and the incidence rate of adverse events were assessed. *Results:* The average cannulation time for the first 5 minutes was 189.7 (2-300) seconds in group PO and 237.8 (2-300) seconds in group NS (P = 0.03). The final success rate of biliary cannulation was 98.8% in group PO and 100.0% in group NS. The incidence rate of post-ERCP pancreatitis was 2.5% (2/80) in group PO and 6.3% (5/80) in group NS (P = 0.44). The mean amylase concentration was 177.4 (range 36-1067) IU/L in group PO and 267.5 (range 42-1733) IU/L in group NS (P = 0.04). *Conclusion:* Peppermint oil helps us to cannulate the papilla, shorten the time of cannulation, and reduce the incidence of hyperamylasemia after ERCP.

Keywords: Peppermint oil, endoscopic retrograde cholangiopancreatography, cannulation time, pancreatitis

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is widely used for the diagnosis and treatment of pancreatobiliary disease, but it requires experienced endoscopic techniques, especially cannulation of the common bile duct (CBD). Even experienced endoscopists do not always achieve deep cannulation of CBD quickly and easily. In addition, ERCP has some complications, especially post-ERCP pancreatitis (PEP). PEP is the most common adverse event following the ERCP, ranging from 3% to 15% according to most literature reports, and it can cause substantial morbidity, mortality, or high medical costs [1, 2]. One of the most important risk factor for PEP is exactly difficult biliary cannulation, especially multiple attempts (greater than 10 attempts) at cannulation [1, 3, 4]. The cannulation time has been reported as a more accurate measure of cannulation difficulty in ERCP than the number of attempts and represents the operator's ERCP experience [5, 6].

Peppermint oil, which has always been used as a herbal medicine, food additive and cosmetics ingredient, has been reported to have the function of inhibiting the contraction of smooth muscle of the gastrointestinal tract [7-9]. Therefore, peppermint oil has been used as an antispasmodic for endoscopic and radiological examinations [10-15]. It is an effective drug for the treatment of abdominal pain, especially irritable bowel syndrome (IBS) and functional dyspepsia (FD) [16-19]. It has also been shown to be a harmless and effective antispasmodic in ERCP [20].

Thus, we hypothesized that peppermint oil can relax both gastrointestinal smooth muscle and

Table 1. Patient characteristics

Characteristic	Group PO	Group NS	*p* value
Number of patients	80	80	
Median age (range) (years)	70.9 (23-97)	72.0 (32-95)	0.71
Sex: male/female	39/41	45/35	0.34
Periampullary diverticulum	23	28	0.40
Bile duct stone			
Pancreatic cancer	2	3	1
Bile duct cancer	1	1	0.48
Gallbladder cancer	1	0	1
Cholecystitis	5	8	0.39
Others (benign bile duct stricture)	3	1	0.61
Others (malignant bile duct stricture)	1	2	1

Oddi sphincter, which can shorten the cannulation time of the papilla. The purpose of this study was to evaluate the efficacy and safety of peppermint oil for the cannulation during ERCP.

Patients and methods

Patients

160 consecutive patients undergone ERCP for suspected of pancreatobiliary disease by examinations (abdominal ultrasonography, computed tomography (CT) scan, or magnetic resonance cholangiopancreatography) were evaluated in this study from June 2016 to April 2017. Exclusion criteria including: less than 18 years of age, the clinical evidence of serious diseases such as acute pancreatitis, taking Anticholinergic drugs or glucagon, peppermint oil allergy, duration of pregnancy and lactation. Patients with the history of ERCP, prior surgery of Billroth II or Roux-en-Y gastric bypass were also excluded.

All enrolled patients were randomly assigned to Peppermint oil group (group PO) and Normal saline group (group NS).

Study design

It is a single-center, prospective, open-labeled, randomized, controlled trial. The study was approved by the ethics committee of YUEYANG Hospital and an informed consent document was obtained from all enrolled patients.

Preparation of peppermint oil solution

Peppermint oil was prepared as a 1.6% solution (8 mL peppermint oil [Xuesong natural medicinal oil Co., Ltd, Jiangxi, China] diluted in 500 mL of Normal saline emulsified by 1 g Sorbitan stearate [Xibao Bio Technologies Inc, Shanghai, China]) and kept at 4°C.

Procedure of ERCP

All ERCP procedures were performed by the same one skilled endoscopist using Olympus JF-260 duodenoscopes (Olympus Corporation, Tokyo, Japan). Before the operation, 5 mg diazepam and 50 mg pethidine hydrochloride were used to perform intravenous conscious sedation. After insertion of the duodenoscope and finding the duodenal papilla, 20 mL of prepared peppermint oil solution (group PO) or Normal saline (group NS) was sprayed on the papilla by syringe via the working channel.

Cannulation was performed using triple-lumen sphincterotome preloaded with a 0.035 guide wire (Boston Scientific Corporation, Natick, MA, USA). The cannulation time was defined as the time from starting cannulate the papilla to the time when the guide wire had been cannulated deeply into the CBD, so that therapeutic procedures could be followed as we need. During the selective CBD cannulation process, if the pancreatic duct was cannulated, the endoscopist would quickly pull back the guide wire from the pancreatic duct and continue deep CBD cannulation. In such a situation, the deep CBD cannulation time count was continued [5]. If the time of selective deep CBD cannulation process exceeds 5 minutes, the endoscopist would change to double-guide-wire technique in patients who achieved unintentional main pancreatic duct insertion or pre-cut with needle knife in patients who failed to cannulate the pancreatic duct.

Outcomes

The primary outcome of the present study was the deep CBD cannulation time. Secondary outcome was success rate of CBD cannulation includes the patients whose CBD were successful cannulated in 5 minutes or exceed 5 minutes by double-guide-wire technique and pre-cut with needle knife. Incidence rate of

Table 2. Cannulation time, cannulation success and complication rates

Variable	Group PO	Group NS	*p* value
Number of patients	80	80	
Success rate for the first 5 minutes (%)	61 (76.0)	52 (65.0)	0.12
Cannulation time for the first 5 minutes, seconds (range)	189.7 (2-300)	237.8 (2-300)	0.03
Success rate of the second method (%)	18 (94.7)	28 (100.0)	0.90
Final success rate (%)	79 (98.8)	80 (100.0)	1.0
Complication rate (%)			
Mild pancreatitis	2 (2.5)	5 (6.3)	0.44
Mean amylase level, IU/L (range)	177.4 (36-1067)	267.5 (42-1733)	0.04

hyperamylasemia and PEP were recorded. Other adverse events related to ERCP including bleeding, perforation, abdominal pain, fever, cholecystitis, or cholangitis were also recorded in detail.

PEP was defined as an emerging pancreatic-type abdominal pain of more than 24 hours, associated with serum amylase elevation to more than 3 times upper limit of normal within 24 hours after ERCP. Abdominal CT images were performed to identify patients with PEP who had severe abdominal pain with elevation of amylase or lipase levels, or leukocytosis. Definition of Asymptomatic hyperamylasemia was at least a 3-fold rise in serum amylase without epigastric pain at 24 hours after the procedure.

Statistical analysis

The data in each patient group are expressed as medians (range) and frequencies. Fischer's exact statistical tests or Student's t-test were used by SPSS v19.0. *p* value of less than 0.05 was set as statistically significant.

Results

Patient characteristics are shown in **Table 1**. A total of 160 patients requiring selective biliary cannulation were enrolled in the study. They were randomly assigned to the group PO (n = 80) and the group NS (n = 80). Baseline characteristics between the two groups were well balanced. The incidence of periampullary diverticula, which is believed as a main risk factors for difficult cannulation, showed no statistically significant difference between the two groups (group PO: 28.8%, group NS: 35.0%, *P* = 0.40).

Table 2 shows the average cannulation time, the cannulation success rates, and complication rates. The success rate of biliary cannulation the first 5 min was 76% (61/80) in group PO and 65.0% (52/80) in group NS (*P* = 0.12). The average cannulation time for the first 5 minutes was 189.7 (2-300) seconds in group PO and 237.8 (2-300) seconds in group NS (*P* = 0.03). Of 19 patients who failed to cannulate the CBD in group PO, 18 were successfully cannulated into CBD after switching to double-guide-wire technique or pre-cut with needle knife, and the remaining one had cannulation failure despite a variety cannulation methods had been used because of malignant ampullary tumor. In group NS, 28 patients who failed to cannulate the CBD were switched to double-guide-wire technique or pre-cut with needle knife and all patients were successfully treated. The final success rate of CBD cannulation was 98.8% in group PO and 100.0% in group NS (*P* = 1.0). PEP (all mild pancreatitis) was observed in 7 patients (4.4%), 2 (2.5%) in group PO and 5 (6.3%) in group NS respectively (*P* = 0.44). The mean amylase concentration was 177.4 (range 36-1067) IU/L in group PO and 267.5 (range 42-1733) IU/L in group NS (*P* = 0.04).

Discussion

For many novice endoscopists, deep cannulation of the CBD during ERCP was seen as a huge barrier. It also represents a technical challenge even to skilled endoscopists [21-23]. In fact, the most common cause of a failed ERCP is the failure of CBD cannulation [22, 23]. Previous studies have reported that difficult cannulation is an important risk factor for ERCP-related complications, such as PEP [1, 4, 22]. To some extent the degree of cannulation

difficulty during ERCP procedure is positively related to PEP [22]. There are many studies which evaluated the degree of cannulation difficulty during ERCP [24-31]. Many endoscopists use the number of cannulation attempts or cannulation time as the evaluation of cannulation difficulty. Recently cannulation time is considered to be a more objective and accurate evaluating indicator for grading cannulation difficulty than the number of cannulation attempts [5].

ERCP is a time-consuming procedure. It is important to inhibit the duodenal peristalsis to guarantee a successful performance. Antispasmodics such as scopolamine or glucagon are used to get the duodenum relaxation for this reason [32]. But these pharmaceutical agents are often associated with some adverse event, such as tachycardia, urinary retention or tremor after scopolamine administration, and delayed hypoglycemia after glucagon administration. In addition to possibly causing nausea and vomiting, glucagon is an expensive drug and still not available in China.

As far as we know, this is the first RCT assessing the effectiveness of Peppermint oil on cannulation time of ERCP. Peppermint oil is a volatile oil extracted from the *Mentha piperita* and has been used as a food additive, cosmetic and herbal medicine for many years [33]. Studies have shown that it can reduce the contractions of smooth muscle in frequency and intensity and provides gastrointestinal relaxation by intraluminal or oral administration [7]. Thus, it has been used as an antispasmodic in the examination of gastrointestinal endoscopy and barium enema [10, 11, 15, 34], and in the treatment of FD and IBS [16-18]. Peppermint oil has also been reported as a harmless antispasmodic for ERCP [20]. Our study focuses on the effectiveness of applying Peppermint oil in cannulation during ERCP.

Data from this study shows that Spray of Peppermint oil on papilla can shorten the cannulation time of ERCP and reduce the post-ERCP mean amylase level, but not significantly reduce the occurrence rate of acute pancreatitis, which may be due to the small sample size. We speculate that the Peppermint oil not only has antispasmodic effect on gastrointestinal smooth muscle, also has a similar effect on sphincter of Oddi, which makes the cannulation easier. At the same time, it may also have relaxation effect on the outflow of the pancreatic duct, thereby reducing the hyperamylasemia and pancreatitis after operation.

To prevent the operator-dependent bias, all the ERCP procedures were performed by one endoscopist. Thereby we can distinguish the results due to techniques performed by the different endoscopist from the other factors. But the present study still has some limitations. First, since the sample size is relatively small, the results of this study are limited and large-scaled prospective randomized multicenter studies should be performed in the future. Second, as an independent risk factor for PEP, sphincter of Oddi dysfunction (SOD) was not evaluated in the present study. We do not know whether peppermint oil has the similar relaxation effect on Oddi sphincter dysfunction. Third, to prevent the confounding factor in our study, indomethacin was not used in any patients, despite the preventive effect of rectal indomethacin on the development of PEP has been proved in previous studies [35, 36]. However, it is what we also want to know whether the effect is better in combination with peppermint oil and indomethacin suppository.

Conclusion

Peppermint oil helps us to cannulate the papilla, shorten the time of cannulation, reduce the incidence of hyperamylasemia after ERCP, or probably even prevent the post-ERCP pancreatitis. Peppermint oil is cheap, easily obtained and convenient to use. It may be feasible as the regular drug for ERCP. Of course, a large-scaled prospective randomized multicenter study is needed to validate the outcomes of our preliminary study.

Disclosure of conflict of interest

None.

Abbreviations

ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; CBD, common bile duct; CT, computed tomography; NS, Normal saline.

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