Sphincter of Oddi Dysfunction and its Therapy with Botulinum Toxin

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Abstract

Achalasia of sphincter of Oddi (SO) when the bilipancreatic juice needed is called dysfunction of sphincter of Oddi (SOD). It can be divided into three types. The pathophysiology, manifestations, diagnosis and therapies of this syndrome are described in this paper. Generally, the patients of SOD have a good response to botulinum toxin therapy. It is said that there is no apparent side effect fond in the therapy.

Pancreatic bile duct terminal, common passage and duodenal papilla are all surrounded by smooth muscles with different thickness, the sphincter of Oddi (SO) which length is 4 – 6 mm. The disorder that SO cannot normally relax, the conduction of bile and / or pancreatic juice is not smooth thus leads to accumulation of bile and / or pancreatitis, which expressed as epigastric pain with repeated attack, icterus, rise in amylase, etc. is called dysfunction of sphincter of Oddi (SOD). Generally, SOD is classified into stenosing type and functional type. The former includes fibrosis, hypertrophy, chronic papillitis and adenitis; the latter includes over-speed of movement, increase in base pressure during systolic, too many reverse contraction, abnormal reaction of SO towards CCK. Clinically, SOD can be classified into 3 types: Type I: most are organic stenosis, expressed as classical bile colicky pain, enzyme of liver (ALP, γ – GT) increases for 1.5 – 2 folds, ERCP has obstructive expression, common bileduct ≥ 12mm, delay excretion > 45min, manometric of bile duct indicates increase of base pressure. Type II (intermediate type): usually process bile colicky pain, only 1 item of the above examination indices is abnormal. Type III (functional type): only process bile pain but no other abnormality[1].

1. The Pathophysiology and Expression

The mechanism of SOD has not yet been cleared. International scholars processed quite many investigation for the pathophysiology of SO. Burton[2] thought that the

recurrence of epigastric pain after cholecystectomy which cause could not be confirmed by radiography and endoscopy (including ERCP) was called postcholecystectomy syndrome, mainly caused by SOD. In 1988, Goff[3] described the physiology and pathophysiology of SO as a high pressure region located in common bileduct, major pancreatic duct and junction of duodenum that processed temporal contracting function. Dysfunction of SO can lead to bile pain and recurrent pancreatitis. Results of animal tests indicated that the pathogenic mechanism of acute alcoholic pancreatitis involves strong stimulation of external secretion, but not related to obstruction or contraction of SO[4]. Zhou *et al.*[5] thought that octreotide and growth inhibitor could both reduce gall bladder pressure in rabbits and reduce electromyographic activity of SO, but intravenous injection of octreotide could not affect the increased SO electromyographic activity and gall bladder pressure that caused by CCK-8 and electric stimulation on dorsal nucleus of vagal nerve. Tanaka *et al*[6] performed morphine intramuscular injection for patients before operation of cholecystectomy to make SO spasm, the pressure inside bile duct would not be changed; however, after intravenous injection of tintinnida, the pressure inside bile duct increased as gall bladder contracted. After the operation, morphine could lead to increase in bile duct pressure with irregularly fluctuation, this might indicate that tintinnida could immediately reduce the pressure and make the irregularly contraction disappear. This indicated that when tintinnida made the gall bladder contract, SO relaxed. As a pressure counterbuff, gall bladder could compensate the SO spasm caused by morphine, which may partially explain the pathogenic mechanism of postcholecystectomy syndrome. For the patients after operation of cholecystectomy with Irritable Bowel Syndrome, SO processed abnormal reaction towards CCK, which indicated that SOD was related to increase in SO sensitivity[7]. Chen *et al*[8] thought that forceless in contraction of gall bladder and SO chalasia was not probably the only direct factor of poor evacuation of gall bladder in Irritable Bowel Syndrome patients. They used the method of real time ultrasound to prove that Domperidone could obviously improve the condition of gall bladder evacuation. They also thought that Domperidone could probably reduce the risk of formation of cholelithiasis.

Increase of pancreatic duct pressure which is alcoholic or with chronic pancreatitis accompanied by papillitis might be caused by dysfunction of papilla, but it could not apply in the case of primary chronic pancreatitis[9]. The pain of alcoholic chronic pancreatitis might not caused by increase in pancreatic duct pressure[10], and the over-length common duct being blocked by gallstone, protein embolus and SOD might be the reason of acute recurrent pancreatitis. At period of no symptoms, the pancreatic duct with no abnormal changes[11]. Tarnasky *et al*[12] proved that the

probability of having chronic pancreatitis for SOD patients was 4 folds higher than that of people who did not have this disease. 20/68 of SOD patients had structural evidence of chronic pancreatitis, 20/23 patients of chronic pancreatitis processed SOD. Among the patients with pain of gall bladder and pancreas which could not be explained, SOD was related to changes of chronic pancreatitis. Guelrud *et al*[13] observed 18 cases (28%) of abnormality in pancreatic-bile duct junction among 64 cases of 1 – 17 years-old recurrent pancreatitis, the lengths of common ducts and sphincter muscles were longer, among those 7 cases processed choledochocyst, and it was thought that recurrent pancreatitis and abnormality in pancreatic-bile duct junction in children and teenagers were related to SOD. Patients of epigastric pain after cholecystectomy were easily to be misdiagnosed as SOD. Some had formation of lithiasis that caused by abnormal conduction from hepatic duct to stump cystic duct, some were caused by adhesion of liver and stomach and compression of gastric antrum by teres ligament of liver[14], some expression of SOD patients after cholecystectomy was like heartstroke[15], some cases of papilla stenosis or primary recurrent pancreatitis were related to celiac disease[16]. Cholecystectomy and isolation of tissue surrounded common bile duct would lead to expansion of common bile duct after operation. This indicated that during operation of bile passage, one should avoid isolation of surrounding tissue of bile passage to prevent appearance of SOD symptoms[17]. Female SOD patients had the tendency of somatization (mental state and experience changed into somatic symptoms) disturbance. For female SOD patients, one should aware for the procession of psychological therapy[18]. Desautels *et al*[19] proved that the disease of type III patients was expressed as hyperalgesia of duodenum, all patients expressed high level of somatization , inhibition, obsessive behavior and anxiety. It was thought that abdominal pain in some type III SOD patients was caused by hyperalgesia of duodenum but not related to bile passage.

For the common bile duct of gall bladder lithiasis and bile-origin pancreatitis patients, the backflow increased obviously, which indicated that the SO functional stenosis was caused by passage of gallstone through bile duct, and leaded to common duct transportation of pancreatic bile duct but not SO incompetence[20]. After cholecystectomy, the serum gastrin level and basic gastric acid secretion of symptomatic group were higher than that of non-symptomatic and normal control group. The symptomatic group performed high dynamic, which indicated that SO high dynamic and high serum gestrin level might be the important factors for the postcholecystectomy syndrome[21]. The results of study in common bile duct hydrostatic force and SO dynamic of 9 cases female SOD patients by Rolny *et al*[22] indicated that the increase in hydrostatic pressure leaded to complete inhibition of SO

temporal contraction, which was consistent with animal (cat) experiments. It was thought that cholecystectomy changed SO dynamic rule of some patients, this mechanism might lead to abdominal pain after cholecystectomy. Patients with abdominal pain but not morphological abnormality usually processed bile duct dynamic disturbance [23]. Guelrud *et al*[24] discovered that in patients of Chagas' disease, the basic SOP, average common bile duct duodenum gradient pressure and SO contraction amplitude increased obviously, which indicated that the Chagas' disease that with abnormal basic SOP pressure might had focal preganglionic neurofibers damage, and the inhibitory pastganglionic neurofibers at least was partially kept intact. The patients of bile backflow gastritis had disturbance in evacuation of gall bladder, it might be related to forceless in contraction of gall bladder or/and disturbance in relaxation of SO[25]. Wei *et al*[26] studied SO dynamics and ultramicro structure of rabbits with early stage gallstone disease and high blood cholesterol level, and discovered that the warping of microfilament and disturbance of node in muscle cells, which indicated that SO was under spasmodic condition, weakening of dynamic function resulted in and emphasize accumulation of bile; swelling of nucleolus might be one of the major factors of increase of SO pressure. Zhang *et al*[27] successfully processed in vitro culture of rabbit SO smooth muscle cells, which purity > 90%, provided a new method for further related study of SO.

2. Diagnosis of SOD

The ways of diagnosis of SOD includes CT, MRI, Bultra, isotope scanning of hepatic, SO manometric, etc. Morphine stimulation test, Quality analysis of bile fluid mechanics (QHBS), CCK or CCK analogs combine with QHBS method, isoamyl nitrate enhancing hepatic isotope mark scintiscanning are all used to identify SO stenosis and SO dyskinesis. These methods have complementary action. Most documentations thought that SO manometric had higher value for diagnosis of SOD[1,28 – 31], but the success rate was 75% only, the occurrence of pancreatitis was 1 % - 5 % [1]. Bortolotti *et al*[32] examination the SOP and pressure of end of bile duct of patients of epigastric pain which did not process either lithiasis or cholangitis after cholecystectomy, all were higher than that of control group. It was thought that this kind of manometric was good in identification of functional papilla stenosis of postcholecystectomy syndrome and epigastric pain caused by other reasons, had guidance function for selectively endoscopic papilla sphincter section (EST). SO manometric had very good repeatability for diagnosis of SO stenosis, but not for SO dynamic abnormality. It was because for all types, the basic SOP could probably increase (especially for type II), which sometimes made manometric hard to identify early organic or functional SOD. It might be the phasal characteristics of abnormal

SO dynamic itself[1,33]. Generally, SOP>5.33kPa was treated as diagnosis standard of SOD, and SOP>4.67kPa was also treated as diagnosis standard by some people[13], but Goff JS[34] observed that the sphincter muscle resting pressure in 21 cases of SOD patients were all less than 5.33kPa.

Internal pressure of bile duct was well related to SOP, since it was easier to do the manometric test of bile duct than that of SO, it could be used as replaced examination of SOD[35]. Manometric test of gastric antrum duodenum could be used as a basic supplementary examination for oddi sphincter manometric test in evaluation of right epigastric pain which reason was not known[36]. Soffer *et al*[37] reported dynamic manometric test for duodenal jejunum for patients that processed bile duct sphincter incision and pancreas fistulation, and thought that the sustain of symptoms after endoscopic pancreatic bile duct sphincterotony was related to the dynamic abnormality of small intestine, this might be one of the reasons of bad curative effect of EST therapy. Hepatic duct scanning counting was a better way of non invaded examination method for diagnosis of suspected SOD cases after cholecystectomy, the sensitivity and specificity could both achieve 100%[38]. And the gall bladder excretion score had no obvious relation with SOP, and could not be used in identification of hepatic pain[39]. It was used thought that ERCP injection of contrast medium initiated pain test could be used to diagnose SOD, but Schmalz *et al*[40] processed bile duct conduction for 224 suspected SOD patients of postcholecystectomy syndrome, width of common bile duct, related study of SOP, and thought that use of these stimulation tests for SOD diagnosis was not reliable.

3. Botulinum Toxin Injection Therapy for SOD

At present, the main therapies for SOD include botulinum toxin (BTX) injection therapy, EST, saccule expansion and placement of supporter inside bile duct[41]. There was a wide variety of SOD therapy because it was still not clear whether SOD was an anatomical pathologic change or a kind of physiological dysfunction. Patients that were not suitable in using EST could use calcium passage repressor or long-acting nitrate preparation[2], aminophylline could reduce the pain caused by SO spasm and increase in amylase and/or alanine aminotransferase that caused by morphine. Combination use of long acting aminophylline with nitrate drugs could prevent nitrate tolerance and intolerance and could prevent duodenal papilla stenosis and formation of adenomatosis if used in therapy of postcholecystectomy syndrome. Saccule expansion could be used in treating surgical sphincteroplasty or recurrent pancreatitis caused of EST failure[44]. EST could relieved pain in most papilla muscle stenosis or spasm patients[2,13,23,31,45], and some obtained satisfactory long term curative effects[31].

EST processed good curative effect for 1 – 17 years old patients of recurrent pancreatitis or SOD that assembled heartstroke[13,15]. EST and cholecystectomy assisted with the smallest medical therapy, the total efficacy for intact gall bladder SOD was 68%[45]. Patients that processed bile duct sphincterotomy but without remission were mostly pancreatic duct sphincter dysfunction or abnormal dynamic of small intestine, should be processed therapies such as pancreatic septostomy[35]. The reason for recurrence of bile colic in patients whose gallstone was completely cleared by lithoclasty and litholytic therapy was the recurrent of gallstone or SOD, the patients should be processed cholecystectomy or EST therapy[46]. The percentage of complication on the day of EST therapy for SOD was 0 – 50%, the admission rate caused by complications was 5.7%[47]. EST might be harmful to SOD patients whose common bile duct did not expand[48]. Jiang *et al*[49] processed EST for 47 patients who had no response towards medical therapy after procession of cholecystectomy, the efficacy was 92.5%. The common bile duct shrunk to normal size, serum ALP and γ-GT decreased. It was thought that ERCP was the main diagnosis method for SOD, manometric test had very high value for SOD diagnosis. For sub-clinical SOD, medical therapy was the first choice, and procession of EST for stenosis type of SOD could obtain satisfactory short term effect.

After placement of supporter, remission of symptoms could probably help in diagnosis of consequently spasmodic SOD, but since the occurrence of pancreatitis was too high, it was not suitable to be used as routine method[34]. After pancreatic duct sphincterotomy, nasopancreatic drainage was processed overnight, the effects and complications were similar to that of placement of supporter after section of pancreatic duct, and there was no need to put out the supporter under the endoscope, and would not lead to damage of pancreatic duct vessel and parenchyma[50]. Surgical sphincteroplasty, sphincteroplasty through duodenum and septostomy through papilla all processed good effects in treatment of SOD, the latter was only suitable for those with Oddi symptoms and/or patients of postcholecystectomy syndrome but not those accompanied with pancreatitis[2, 51]. Animal tests and clinical experience indicated that vagotomy might be an option of therapy for postcholecystectomy syndrome caused by SOD and idiopathic recurrent pancreatitis. Yinchenhao Tang Oriental Wormwood Decoction combined with EST had good effect in treatment of acute cholangitis accompanied with endotoxicemia. The action of Chinese medicine in treatment of SOD is worth investigation. BTX could block release of acetylcholine in nerve muscle junction thus made the smooth muscle relax. Recently, it was used in SOD. Sand *et al*[55] proved that local injection of BTX could make piglets SOP decreased for about 50%, potassium chloride, extrinsic acetylcholine, electric stimulation could

lead to apparent contraction of exsomatize SO. Atropinum could block the SO contraction caused by acetylcholine but BTX could not. It was thought that the action mechanism of BTX for smooth muscle was the same as that of skeletal muscle, that is, produced muscle paralysis action through inhibition of releases of presynaptic acetylcholine, and had no effect on postsynaptic muscarin receptors. Wang *et al*[56] injected BTX into duodenal papilla, and the basic pressure, amplitude and dynamic all obviously decreased during each phase of duodenal complex wave migration, the effects lasted for about 7 months. BTX had been used in treatment of many muscular spasm disorders, such as blepharospasm, facial spasm, strabismus, spasmodic torticollis, achalasia, etc and obtained better effects[57,58,59]. By the same principle, it could reduce SO pressure and be used in treatment of SOD, relieved some bile abdominal pain and treated recurrent pancreatitis.

Although BTX could improve SO dynamic and bile excretion after cholecystectomy, the relief in bile type pain was very little, EST procession could not obtain satisfactory remission of symptoms[60,61]. For a group study of 3a, there were 22 cases of type III SOD patients with epigastric pain after cholecystectomy, who were processed endoscopic one-injection of 100μ BTX into ampulla papilla, after 6 weeks there were 12 cases (55%) had symptom remission; after 6 months, the effect lasted in only 1 cases, and the symptoms of the other 11 cases appeared again, SOP rised, after procession of EST, the symptoms relieved and lasted for 15 months without recurrence. Among the 10 cases that without remission, there were 5 cases whose base SOP back to normal (<4.67kPa), the EST later on still could not improve these 5 cases, but EST processed remission in other 2 cases whose SOP were still high. It was thought that patients with good response towards BTX treatment also had better response towards EST[62]. The results of treatment for a case of recurrent pancreatitis by Muehldorfer *et al*[63] also supported this point of view.

Most reports thought that the therapeutic dosage BTX had no obvious toxic effect[55-61]. Histology examined removed SO after BTX injection, no obvious pathologic change was found, which indicated the safety of BTX[55]. However, Schnider *et al*[64] reported a case of 43 years old blepharospasm female patient without gall bladder medical history, repeatedly used BTX local injection therapy for many times within 6a and processed paroxysmal biliary colic after 3 weeks of each treatment; after performing cholecystectomy, no biliary colic occurred again. In other 4 cases of spasmodic torticollis, abnormality evacuation of gall bladder occurred at day 5 and day 15 after injection of 12.5ng of BTX, whereas for the 2 cases of blepharospasm accepted injection of 1.20ng or 2.5ng of BTX, no such abnormality

occurred. Thus it was thought that BTX had the dosage-dependent weakening effect of gastrointestinal autonomic nerve passage, which might delayed evacuation of gall bladder and leaded to bile accumulation of bile. Therefore, when repeatedly used BTX for many times, one should be aware of the dosage accumulative gastrointestinal side effects, especially for the patients accompanied with gall bladder disorder.

In conclusion, since the pathogenic mechanism had not been cleared, and there were many ways of therapy, BTX injection into duodenal papilla as a non-invasive therapy with no obvious side effect still have no reports in China, its situation in treatment of SOD worths further study.

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