

Using cholecystokinin to facilitate endoscopic clearance of large common bile duct stones

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Abstract

AIM: To evaluate the effect of cholecystokinin (CCK) during extracorporeal shockwave lithotripsy (ESWL) in the clearance of common bile duct (CBD) stones in endoscopic retrograde cholangiopancreatography (ERCP).

METHODS: Between January 2007 and September 2012, patients with large CBD stones who were treated with ESWL and ERCP were identified retrospectively. Patients were randomized in equal numbers to cholecystokinin (CCK) and no CCK groups. For each CCK case, a dose (3 ng/kg per min for 10 min) of sulfated octapeptide of CCK-8 was administered intravenously near the beginning of ESWL. ERCP was performed 4 h

after a session of ESWL. The clearance rate of the CBD was assessed between the two groups.

RESULTS: A total of 148 consecutive cases (CCK group: 74, no CCK group: 74) were tallied. Overall there were 234 ESWLs and 228 ERCs in the 148 cases. The use of CCK showed a significantly higher rate of successful stone removal in the first ESWL/ERCP procedure (71.6% vs 55.4%, $P = 0.035$), but resulted in similar outcomes in the second (42.8% vs 39.4%) and third (41.7% vs 40.0%) sessions, as well as total stone clearance (90.5% vs 83.8%). The use of mechanical lithotripsy was reduced in the CCK group (6.8% vs 17.6%, $P = 0.023$), and extremely large stone (≥ 30 mm) removal was higher in the CCK group (72.7% vs 41.7%, $P = 0.038$).

CONCLUSION: CCK during ESWL can aid with the clearance of CBD stones in the first ESWL/ERCP session. Mechanical lithotripsy usage was reduced and the extremely large stone (≥ 30 mm) clearance rate can be raised.

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Key words: Common bile duct stones; Extracorporeal shockwave lithotripsy; Endoscopic retrograde cholangiopancreatography; Cholecystokinin

Core tip: Extracorporeal shockwave lithotripsy (ESWL) and endoscopic retrograde cholangiopancreatography (ERCP) are frequently used for patients with large common bile duct (CBD) stones. Cholecystokinin can relax the sphincter of Oddi by binding to its inhibitory receptors. The effect of cholecystokinin (CCK) during ESWL on CBD stone clearance in the following ERCP has not previously been reported. The results of our research suggested that CCK during ESWL can aid the clearance of CBD stones in the first ESWL/ERCP session. Additionally, mechanical lithotripsy usage was reduced and the extremely large stone (≥ 30 mm) clearance rate can be raised.

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INTRODUCTION

The prevalence of common bile duct stones increases with age, and their treatment is difficult. Endoscopic retrograde cholangiopancreatography (ERCP) is a well-established standard method for treating common bile duct stones^[1]. This technique was initially introduced by Kawai *et al*^[1] in 1974. About 80% to 90% of common bile duct (CBD) stones can be extracted using conventional techniques such as via a retrieval basket or balloon catheter^[2-4]. Among the reasons for failure of conventional endoscopic therapy are impacted stones, extremely large stones, stones located intrahepatically, or stones proximal to bile duct stenosis. Extracorporeal shock wave lithotripsy (ESWL) was first introduced in the 1980s for the fragmentation of renal and ureteric calculi^[5]. Its application was quickly extended to large biliary and pancreatic stones. Sauerbruch *et al*^[6] proved the efficacy of ESWL in successfully fragmenting CBD stones in about 90% of patients with mild complications.

Cholecystokinin (CCK) is a member of the 'gut-brain' family of peptide hormones. It performs many regulatory functions in the gut and brain by binding to G-coupled CCK receptors located on the target organs. CCK-1 receptors are present primarily in the gastrointestinal tract, myenteric plexus, and vagal afferents, while CCK-2 receptors are present primarily in the brain. CCK-1 is highly specific for binding sulfated CCK, while CCK-2 binds gastrin and CCK with equal affinity. Sulfated octapeptide of CCK-8 binds CCK-1 receptors located on the smooth muscle wall of the gallbladder, making the gallbladder contract and secreting bile into the intestine. It simultaneously relaxes the sphincter of Oddi by binding to its inhibitory receptors^[7,8]. There are reports that diuresis during ESWL for ureteral stones resulted in superior stone fragmentation and clearance compared with standard ESWL^[9,10]. The presence of a fluid interface between the ureteral wall and the stone was reported as an important factor for successful stone fragmentation^[11]. In addition, there is a report that the initial shocks cause cracking of the outer stone shell which can then cause urine to penetrate deeper into the stone, thus making an internal fluid/stone interface^[12]. Therefore, we hypothesized that CCK may aid fragmentation of CBD stones by creating a fluid-filled space at the circumference or within stones, thereby enhancing the coupling of shock waves. The effect of CCK during ESWL on CBD stones has not previously been reported.

The aim of this study was to evaluate the effect of

CCK administered during ESWL on the clearance of CBD stones at ERCP.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of Zibo Central Hospital. It was conducted at the Department of Gastroenterology in Zibo Central Hospital, which is a tertiary referral hospital in Zibo, Shandong Province, China. All patients signed informal consent for the endoscopic procedures and ESWL treatment. The inclusion criteria were adult patients with CBD stones who underwent an unsuccessful initial ERCP due to large stone size. Before ERCP, a nasobiliary tube (NBT) or biliary stent was placed in all patients to irrigate the stones and visualize the calculi during ESWL. The number and diameter of stones were assessed at a pre-ESWL X-ray or computed tomography (CT) scan. If multiple stones were detected, the largest single stone diameter was tallied. Patients were treated with ESWL (14-26 kV) followed by ERCP in the two hospitals. For CCK cases, 3 ng/kg per minute of sulfated octapeptide of CCK-8 (ChiRhoStim™, Bell-More Labs, Inc., Hampstead, MD) was infused over 10 min through an infusion pump before ESWL at the discretion of the managing physician. A high CCK dose is reported to induce cystic duct contraction and the subsequent non-emptying of the gallbladder. About 26% of healthy subjects given 20-40 ng/kg CCK-8 over 3 min develop abdominal pain, and many show no gallbladder emptying at all. ESWL was performed by experienced gastroenterologists using an electro-hydraulic spark gap lithotripter (HealthTronics, Austin, TX). Patients were treated in the prone position and under general anesthesia with continuous monitoring. Common bile duct stones were localized and targeted by an X-ray focusing system. ESWL was carried out at a rate of 90 shocks/min for 10 min at an intensity of 4 (in a scale of 1-6 corresponding to 11000-16000 kV). All patients were subjected to a maximum of 5000 shocks per session, unless the stones were earlier fragmented to less than 5 mm. ERCP was carried out 4 h after a session of ESWL in order to clear the fragments using a retrieval basket or balloon catheter, unless the stone passed spontaneously. Clearance of the CBD was assessed after final procedures with procedure reports, plain films, ERCP films, and/or abdominal CT.

The definition of degree of CBD clearance after ERCP was as follows: Complete successful clearance: CBD stones were successfully fragmented to less than 5 mm in size and more than 90% of fragments were cleared using a balloon or basket. Partial successful clearance: stones were fragmented to larger than 5 mm, there was clearance of more than 50% of the stone volume, and an additional retrieval device such as mechanical lithotripter was required to clear the large fragments. Unsuccessful clearance: stones were fragmented to larger than 5 mm in size and the stone clearance was less than 50%.

Table 1 Baseline characteristics of the patients in the two groups *n* (%)

	CCK group (<i>n</i> = 74)	No CCK group (<i>n</i> = 74)	<i>P</i> value
Age (yr, mean ± SD)	67.5 ± 5.6	69.2 ± 6.3	0.542
Sex (male/female)	40/34	38/36	0.338
Bile duct stricture	32 (43.2)	30 (40.5)	0.292
Pre-cut sphincterotomy	39 (52.7)	40 (54.1)	0.451
Altered anatomy	21 (28.4)	19 (25.7)	0.319
Multiple stones	29 (39.2)	26 (35.1)	0.267
Stone size (mm), mean ± SD	18.6 ± 2.4	17.2 ± 3.4	0.326
≥ 30 mm stone	11 (14.9)	12 (16.2)	0.195

Analysis of characteristics of patients enrolled in the study. Patient baseline characteristics include age, sex, bile duct stricture, pre-cut sphincterotomy, altered anatomy, multiple stones, stone size, and the presence of extremely large stones (≥ 30 mm). There were no significant differences between patients in the cholecystokinin (CCK) and no CCK groups in terms of these characteristics.

Statistical analysis

Data was expressed by mean ± SD. We used the χ^2 test or the Fisher exact test for non-continuous variables and the Student *t* test for continuous variables in the statistical analysis course. SPSS 12.0 (SPSS Inc., Chicago, United States) was used in the analytical procedure. A *P* value below 0.05 was considered statistically significant.

RESULTS

A total of 148 consecutive patients (CCK group: 74, no CCK group: 74) were included in this study. Clinical characteristics are summarized in Table 1. There was no significant difference between the two groups with respect to bile duct stricture (43.2% *vs* 40.5%, *P* = 0.292), pre-cut sphincterotomy (52.7% *vs* 54.1%, *P* = 0.451), stone size (18.6 ± 2.4 mm *vs* 17.2 ± 3.4 mm, *P* = 0.326), altered anatomy (28.4% *vs* 25.7%, *P* = 0.319), and patients who had multiple stones (39.2% *vs* 35.1%, *P* = 0.267) and extremely large stones (≥ 30 mm; 14.9% *vs* 16.2%, *P* = 0.195).

The patient flow diagram is summarized in Figure 1. Overall, there were 234 ESWLs and 228 ERCPs in the 148 patients. Stones passed spontaneously in 6 patients after ESWL treatment, 4 patients in the CCK group, and 2 patients in the no CCK group. In the analysis of the first ESWL/ERCP session, the use of CCK showed a significantly higher rate of complete post-ERCP CBD clearance (71.6% *vs* 55.4%, *P* = 0.035). In the second and third sessions, there was no significant difference in complete stone clearance between the two groups, and it was achieved in 9 of 21 patients (42.8%), 5 of 12 patients (41.7%) in the CCK group; in 13 of 33 patients (39.4%), 8 of 20 patients (40.0%) in the no CCK group. The overall successful stone clearance had no significant difference between the two groups, with 90.5% in the CCK group and 83.8% in the no CCK group, *P* = 0.178 (Table 2). For patients whose stones could not be cleared completely during the first ESWL/ERCP session, the

main reasons were larger stone size, presence of numerous stones, or both. As for the 21 patients in the CCK group, size ≥ 30 mm, number ≥ 5, both size ≥ 30 mm and number ≥ 5, and “other” were identified in 7, 7, 2, and 5 patients, respectively. As for the 33 patients in the no CCK group, the numbers were 8, 13, 4, and 8, respectively. Stones cleared by conventional methods were similar between both groups (92.8% *vs* 90.2%, *P* = 0.315), but the CCK group did show reduced mechanical lithotripsy use (6.8% *vs* 17.6%, *P* = 0.023), and extremely large (≥ 30 mm) stone removal was higher in the CCK group, with 72.7% (8/11) *vs* 41.7% (5/12), *P* = 0.038 (Table 3).

Reasons for failure were impacted stones and stones present above a stricture. These patients were subjected to surgical procedure for stone removal after failed stone clearance in the third ESWL/ERCP session. Post-ERCP complications had no significant difference between the two groups (8.7% *vs* 8.0%, *P* = 0.528). For the 9 patients in CCK group, post-ERCP complications included pancreatitis, cholangitis, and hemobilia, and occurred in 4, 4, and 1 patients, respectively. As for the 10 patients in the no CCK group, the numbers were 5, 3, and 2, respectively (Table 4). Post-ESWL complications included purpuric spots and skin ecchymosis; these needed no treatment and generally disappeared within a week. Severe complications such as splenic rupture, ductal perforation, and necrotizing pancreatitis did not occur in the patients. The most common reversible side effect in the CCK intravenous injection test was upper abdominal pain. There was usually a feeling of abdominal bloating and satiety associated with the symptom. There were some other symptoms including nausea, vomiting, light-headedness, and occasional heartburn. In our study the above adverse effects were mild and no patient had such severe symptoms that the injection had to be stopped due to distress, with all occasional mild discomfort being alleviated by atropine and loxiglumide. There was no procedure-related mortality among patients in our study and no obvious allergic symptom from CCK administration.

DISCUSSION

Bile duct stones may cause jaundice, cholangitis, pruritus, or biliary pancreatitis.

Since the introduction of ERCP in 1974, there has been much progress regarding this procedure for the treatment of CBD stones. Today it has been recognized worldwide as the first-line treatment for CBD stones^[15]. ESWL of bile duct stones can be performed using kidney lithotripters^[14-16], and its efficacy in the treatment of CBD stones has been reported in many studies^[17,18].

Fragmentation alone may or may not be adequate for ductal clearance. To facilitate ductal clearance and decompression, endoscopic therapy is usually performed after ESWL in order to clear fragments and address any ductal strictures by balloon dilation with or without stenting. Accordingly, ESWL overcomes the problem of large-sized stones by fragmenting them and reducing the stone

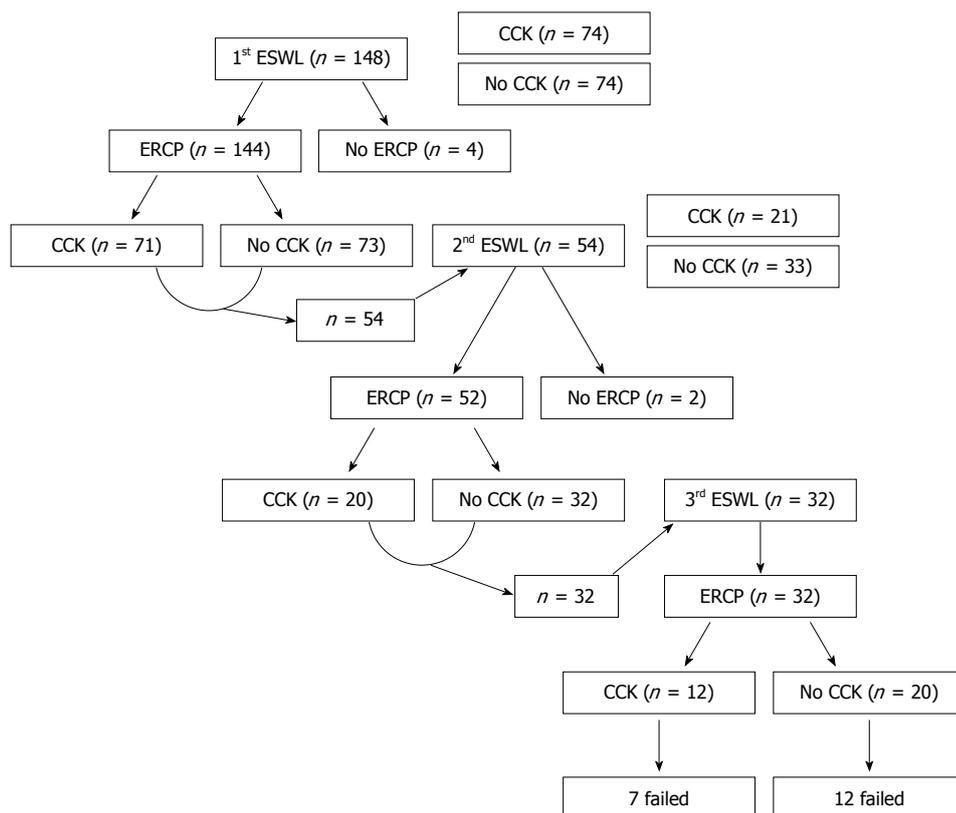


Figure 1 Summarized patient flow in the three sessions of extracorporeal shock wave lithotripsy/endoscopic retrograde cholangiopancreatography procedure. A total of 148 patients in the CCK and no CCK groups were subjected to three sessions of ESWL/ERCP procedure. After a session of ESWL, the common bile duct was cleared by ERCP unless the stone passed spontaneously. Patients that failed to be successfully treated with ERCP were subjected to following ESWL/ERCP treatment. CCK: Cholecystokinin; ESWL: Extracorporeal shock wave lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography; No ERCP: Stone passed spontaneously after ESWL treatment and did not require ERCP treatment.

burden, thus facilitating endoscopic clearance of the bile duct. In the literature, the complete clearance of the CBD can be achieved in 75%-85% of patients^[19,20]. Similarly, our overall complete CBD clearance was 87.2%.

Previous studies have shown improved stone clearance with the use of diuretics prior to ESWL for ureteral stones^[9,10]. In our report, the CCK group showed higher complete CBD clearance than the no CCK group in the first ESWL/ERCP session (71.6% vs 55.4%, $P = 0.035$). We thought the dose (3 ng/kg per minute for 10 min) of sulfated octapeptide of CCK-8 injected intravenously near the beginning of ESWL in our test could cause gall-bladder contraction and secretion of bile and pancreatic fluid into the intestine, as well as simultaneously relaxing the sphincter of Oddi by binding to its inhibitory receptors; therefore it may aid in the fragmentation of bile duct stones by creating a fluid-filled space at the circumference or within stones, thereby enhancing the coupling of shock waves. Bile and pancreatic fluid might facilitate the flushing out of stone fragments during ESWL. The overall complete clearance rate for CBD stones had no significant difference between the two groups, with 90.5% vs 83.8%, $P = 0.178$. Complete CBD clearance in the second and third sessions of ESWL/ERCP treatment did not show a significant difference between the two groups. We thought the number of patients subjected to

second and third sessions of ESWL/ERCP treatment might be too small to have a statistical significance. It also reflected the effectiveness of multiple sessions of ESWL for common bile duct stones in our study. More treatment sessions were to some extent correlated with a greater stone number and a larger size of stones. The stone clearance rate could reach above 80.0% in the two groups by using conventional methods such as balloon and basket. The clearance rate [72.7% patients for CCK group (8/11) vs 44.4% patients for no CCK group (4/9)] of extremely large stones (≥ 30 mm) and the rate of mechanical lithotripsy use (6.8% vs 17.6%, $P = 0.023$) showed a significant difference between the two groups. Our results correspond with those of previous studies concerning overall stone clearance^[21,22]. In our study, the CCK group showed better results in the removal of common bile duct stones in the first ESWL/ERCP procedure and reduced overall mechanical lithotripsy use. Although this difference might be due to various factors (such extent of ERCP, size of stone and the dilating balloon, the shape of the stone, and the bile duct), we think that CCK use is the most important factor in raising the clearance rate of large common bile duct stones and reducing mechanical lithotripsy use.

In previous studies, the presence of a downstream stricture, stone size, and location influenced stone frag-

Table 2 Endoscopic stone removal after extracorporeal shock wave lithotripsy/endoscopic retrograde cholangiopancreatography procedure *n* (%)

Attempt	CCK group (<i>n</i> = 74)	No CCK group (<i>n</i> = 74)	<i>P</i> value
First	53/74 (71.6)	41/74 (55.4)	0.035 ¹
Second	9/21 (42.8)	13/33 (39.4)	0.218
Third	5/12 (41.7)	8/20 (40.0)	0.346
Total	67/74 (90.5)	62/74 (83.8)	0.178

¹Analysis of endoscopic stone removal after ESWL/ERCP procedure in the two groups. Successful stone clearance rate after the first session of ESWL/ERCP procedure showed a significant difference between the CCK group and no CCK group ($P < 0.05$). common bile duct clearance rate after the second and third sessions of ESWL/ERCP procedure and total clearance rate did not show a significant difference. CCK: Cholecystokinin; ESWL: Extracorporeal shock wave lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Extraction methods and success rate after extracorporeal shock wave lithotripsy/endoscopic retrograde cholangiopancreatography procedure *n* (%)

Extraction method	Success rate		<i>P</i> value
	CCK group (<i>n</i> = 74)	No CCK group (<i>n</i> = 74)	
Balloon or Dormia basket	64/69	55/61	0.315
Mechanical lithotripsy	3/5	7/13	0.023 ¹
Stone size			
15-30 mm	59/60	57/62	0.415
≥ 30 mm	8/11	5/12	0.038 ²
Total	67 (90.5)	62 (83.8)	0.178

¹Analysis of extraction methods and success rate after ESWL/ERCP procedure in the two groups. Patients needing balloon or Dormia basket to clear CBD stones did not show a significant difference between the CCK group and the no CCK group, while mechanical lithotripsy usage was significantly different ($P < 0.05$); ²Successful clearance rate of patients with stones 15-30 mm was similar between the two groups, but clearance rate of patients with stones ≥ 30 mm between the two groups show significant difference ($P < 0.05$). CCK: Cholecystokinin; ESWL: Extracorporeal shock wave lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography.

mentation and clearance^[23]. In our study, main common bile duct strictures were balloon dilated in nearly all cases. Such treated strictures were not a negative factor for stone clearance in our study. Previous studies reported there was a significantly improved complete CBD clearance rate in cases with previous biliary sphincterotomy or biliary stent (*vs* no sphincterotomy or stent). It is probable that cases permitting stent placement had lower grade strictures and fewer impacted stones. In our study, a nasobiliary tube or biliary stent was placed in all patients, which may be an important therapeutic effect allowing high complete stone clearance in our study.

The mean number of ESWL sessions per case varied from 2.5 to 5.0 in published series^[24-26]. However, in our study above 80% of patients in the two groups got successful CBD clearance after three sessions of ESWL/ERCP treatment. The equipment to facilitate ERCP has developed in the last few years, which may explain the fewer sessions of ESWL/ERCP in our study. This also

Table 4 Complications in cholecystokinin group and no cholecystokinin group *n* (%)

	CCK group	No CCK group	<i>P</i> value
Complications, post-ERCP	9/103 (8.7)	10/125 (8.0)	0.528
Pancreatitis (mild)	4	5	
Cholangitis (mild)	4	3	
Hemobilia (mild)	1	2	
Bowel perforation	0	0	
Procedure-related mortality	0	0	
Complications, post-ESWL	8/107 (7.5)	10/127 (7.9)	0.673
Purpuric spots	5	6	
Skin ecchymosis	3	4	
Splenic rupture	0	0	
Lung trauma	0	0	
Necrotizing pancreatitis	0	0	
Procedure-related mortality	0	0	

Analysis of complications in CCK group and no CCK group. These include post-ERCP and post-ESWL complications. The overall post-ERCP and post-ESWL complications are not significantly different between the two groups. CK: Cholecystokinin; ESWL: Extracorporeal shock wave lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography.

reflected by experience of ERCP at our hospital when dealing with large common bile duct stones.

Post-ERCP complications (8.7% *vs* 8.0%, $P = 0.528$) and post-ESWL complications (7.5% *vs* 7.9%, $P = 0.673$) had no significant difference between the two groups. Perforation did not occur in all patients. Cholecystitis occurred in 4 and 3 patients in the two groups respectively, and was relieved by antibiotics. The rate of pancreatitis after ESWL/ERCP was acceptable and was low compared to those of other studies^[14,18,27]. In the present study, the bleeding and cholangitis rates were similar to 1% to 3.0% rates reported by Cotton *et al.*^[28] or a MeSH study^[29]. However, the clinical implications and fewer incidences of endoscopically evident bleeding were unclear, and thus further study is needed. Some rare and serious complications have been reported after ESWL^[30-33]. These include perirenal hematoma, biliary obstruction, bowel perforation, splenic rupture, lung trauma, and necrotizing pancreatitis. These severe complications did not occur in our study due to accurate targeting and reduced patient movement. Pain at the site of shock wave delivery, skin ecchymosis, abdominal pain, occasional fever, and hemobilia were observed in some patients. These complications were mild and minimal, with all being managed conservatively without an extension of hospital stay.

Although we routinely used the measure of ESWL combing ERCP to evaluate efficacy and complications in our study, this technique might be more likely useful in specific groups of patients advised by other studies^[34,35]. To confirm efficacy in these situations, more investigations are recommended.

There are several limitations in this study. Firstly, the interpretation for degree of CBD clearance could be subjective. Although this might be possible, all stone clearance results were determined by procedure reports recorded by each endoscopist who was unaware of the use of CCK during ESWL. Stone clearance was confirmed

by pancreatogram or CT. Secondly, the treatment effect might be due to improved physician skill. Other limitations include the study being single center and the relatively small number of patients. Further prospective randomized studies are also needed in order to prove efficacy and evaluate cost efficacy.

In conclusion, CCK during ESWL showed better results than those with ESWL alone in the first session of ESWL/ERCP for removing common bile duct stones, and did not raise any major complications. Moreover, CCK during ESWL also raised the extremely large stone (≥ 30 mm) clearance rate in the final outcome while also reducing mechanical lithotripsy use. Therefore, this measure should be recommended in clinical practice.

COMMENTS

Background

Extracorporeal shock wave lithotripsy (ESWL) uses electromagnetic waves to fragment difficult biliary stones when endoscopic retrograde cholangiopancreatography fails. Cholecystokinin (CCK) is a member of the "gut-brain" family of peptide hormones. An important role of CCK is to stimulate gallbladder contraction, pancreatic secretion, and intestinal motility. It simultaneously relaxes the sphincter of Oddi by binding to its inhibitory receptors. CCK may aid the clearance of common bile duct stones during ESWL.

Research frontiers

Current results in the literature obtained with third generation electromagnetic lithotripters and sulfated octapeptide of CCK-8 are already optimal; however, technological improvements in lithotripters and other factors facilitating stone fragmentation may further enhance performance.

Innovations and breakthroughs

The authors' work emphasizes, in a wide patient population, that CCK during ESWL is safe and effective in clearing common bile duct stones in the first ESWL/endoscopic retrograde cholangiopancreatography (ERCP) session, with extremely large stones (≥ 30 mm) removal being higher in the final outcome and reduced lithotripsy use.

Applications

The study is of interest for physicians dealing with common bile duct stones, particularly those managing extremely large stones (≥ 30 mm) that failed to be removed in the first ERCP procedure. Based on these results, CCK combing with ESWL was confirmed to be the first choice for the treatment of large common bile duct stones.

Peer review

Overall, the study helps to evaluate a role of CCK combing with ESWL in dealing with large and difficult common bile duct stones.

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