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Research Article

Efficacy of Medical Treatment by Glyceryl Trinitrate (GTN) in Management of a Small Stone in the CBD in Patients with Chronic Calcular Cholecystitis due to Spasm in Sphincter of Oddi

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Abstract

Background: Early detection of stones in the common bile duct (CBD) in patients with chronic calcular cholecystitis and adequate management of them are important to decrease patients' morbidity. In some patients a spasm in sphincter of oddi might lead to entrapment of a small stone which could be managed medically without surgical intervention. Glyceryl trinitrate (GTN) was found to dilate blood vessels and sphincter of oddi.

Aims: To evaluate the benefits of using GTN in management of a small stone in the CBD in patients with chronic calcular cholecystitis aiming to avoid unnecessary surgery.

Patients and Methods: We performed our study on 30 patients having chronic calcular cholecystitis with CBD stone. We give them GTN as medical treatment daily for about one week. We followed them for 7 days for clinical, laboratory and sonographic improvement.

Results: We found that 25 (83.3%) of our patients have clinical, laboratory and sonographic evidence of improvement of symptoms in a median time of 4 - 5 days ($p = 0.001$) and then ERCP and cholecystectomy was done later on. While 5 (16.7%) cases revealed elevated pancreatic enzymes which denoted failed medical management with persistence of the stone and needed ERCP then cholecystectomy later on ($p = 0.001$). There was a significant association between patients with succeeded medical treatment and patients with failed medical treatment regarding size of the stone and age of the patient ($p = 0.001$). Ultrasonography showed significant reduction in CBD diameter ($p = 0.001$) during GTN treatment.

Conclusion: Small stone in the CBD might be resulted from a spasm in sphincter of oddi and could be effectively managed by medical treatment using GTN which could result in a clinical recovery of most patients and ERCP and cholecystitis could be done later on.

Keywords: *Chronic Calcular Cholecystitis; Common Bile Duct Stone; Spasm in Sphincter of Oddi GTN Therapy*

Introduction

The presence of a stone in the common bile duct (CBD) has a prevalence of 10-20% in gall stones patients. It was found to be associated with many complications, as obstructive jaundice and acute pancreatitis. Early detection and adequate rabid management of such condition is important to decrease subsequent complications [1]. Although there is marked advancement and refinement of laparoscopic surgical techniques, the management of concomitant stones in the gallbladder and the CBD remains controversial [2]. The sphincter of Oddi (SO) is the smooth muscle which is control the choledochoduodenal junction regulating bile flow and preventing duodeno-biliary reflux. Glyceryl trinitrate (GTN) is an organic nitrate that could be able to relax the blood vessels smooth muscle. Such effect of GTN was widely accepted for angina pectoris management [3]. The sphincter of Oddi dysfunction (SOD) was referred to many biliary, pancreatic, and hepatic disorders which resulted from strictures or spasms of such sphincter [4]. Endoscopic retrograde cholangiopancreatography (ERCP) is now a widely accepted and performed procedure which could have diagnostic and therapeutic purposes. As any surgical interventional modality ERCP carries some risk of morbidity [5].

We hypothesized that in case of spasm of sphincter of oddi or SOD which entraps small stones could be safely managed by GTN and lead to passage of the stone postponing performing cholecystectomy and decreasing incidence of performing ERCP.

Aim of the Study

To evaluate the benefits of using GTN in management of a small stone in the CBD in patients with chronic calcular cholecystitis aiming to avoid unnecessary surgery.

Patients and Methods

1. We performed this prospective cohort study in Departments of; General Surgery, Zagazig University, General Surgery, Benha University and Radiology, Faculty of Medicine Zagazig University.
2. We have obtained an IRB approval from Faculty of Medicine, Zagazig University and Benha University and a written consent from all included patients.
3. We have included 30 patients with clinical, laboratory and sonographic evidences of chronic calcular cholecystitis with CBD stone that were admitted to General Surgery department in the period from May 2016 to May 2019.

Inclusion criteria of patients

1. Middle aged patients with diagnostic criteria of chronic calcular cholecystitis with CBD stone (a) stone size less than 6 mm (b) Ultrasonic evidence of CBD dilation.
2. Patients who refuse to perform ERCP and prefer trying GTN treatment.

Exclusion criteria of patients

1. Old patients with large stone more than 6 mm.
2. Clinical, laboratory or radiological evidence of pancreatitis or rising jaundice.
3. Elevated levels of lipase or amylase enzymes.

Given medical treatment

1. Oral GTN has been given to the patients at a dose of 10 mg twice daily for 4 - 7 days.
2. We monitored the patients clinically, laboratory and radiologically for clinical improvement or deterioration, liver function tests, amylase and lipase levels.

3. Radiological evaluation was done by ultrasound assessment at time of presentation, at 2 days of starting medical therapy and one week of administration of GTN.
4. ERCP and cholecystectomy was performed in cases which revealed failure of medical therapy with persisting stone.

Statistical analysis

We have analyzed data were using Statistical Package for Social Science for windows (SPSS Inc., Chicago, IL, USA). Continuous variables were assessed using Shapiro-Wilk test, we used Mann-Whitney U for non-normally distributed data, we compared percent of categorical variables by using Chi-square test and we considered the P-value < 0.05 statistically significant.

Results

Basic and demographic data of included patients were detailed in table 1.

Basic characteristics and outcome	Calcular cholecystitis patients with stone in the common bile duct (n = 30)	
	No.	%
Sex		
Female	28	93.3%
male	2	6.7%
Age at presentation (years) (Mean ± SD)	25.60 ± 18.98	
Days of medical therapy (days) (Mean ± SD)	4.88 ± 3.62	
Size of the stone (Mean ± SD)	5.32 ± 1.27 mm	
Comorbid condition		
Absent	23	76.7%
Present	7	23.3%
CBD dilatation (mm)		
Before management (Mean ± SD)	4.56 ± 1.55	
After management (Mean ± SD)	2.70 ± 1.08	
Alkaline phosphatase after anti-spasmodic		
High	25	83.3%
low	5	17.7%
Technical success and patient satisfaction		
Present	25	83.3%
Absent	5	17.7%
Outcome		
Failure	25	83.3%
Success	5	17.7%

Table 1: *Basic characteristics and outcome of the studied chronic calcular cholecystitis patients with stone in the common bile duct following glyceryl trinitrate therapy (n = 30).*

n = Total number of patients; Quantitative data were expressed as mean ± SD (standard deviation); Qualitative data were expressed as number (percentage).

Most of our patients (83.3%) were females. Mean ± SD of age =25.60 ± 18.98 years. Size of the stone in the CBD = 5.32 ± 1.27 mm

Table 2 demonstrated factors which determine success of GTN medical management of most of the included patients.

Basic characteristics	Calcular cholecystitis patients (n = 30)		Outcome				p-value
		Failure (n = 5) (17.7%)		Success (n = 25 (83.3%)			
	No.	%	No.	%	No.	%	
Sex							
Female	28	93.3%	4	19%	24	81%	1.000
male	2	6.7%	1	25%	1	75%	
Age at presentation (Mean ± SD)	25.60 ± 18.98		33.00 ± 2.91		27.50 ± 18.08		0.001
Days of medical therapy (days) (Mean ± SD)	4.88 ± 3.62		6.00 ± 1.91		3.35 ± 2.51		0.023
Size of the stone (Mean ± SD)	5.32 ± 1.27 mm		6.32 ± 1.27 mm		3.32 ± 1.27 mm		0.001
Comorbid condition							
Absent	23	76.7%	3	13%	20	87%	0.033
Present	7	23.3%	2	34%	5	43%	
CBD dilatation (mm)							
Before and after management (Mean ± SD)	4.56 ± 1.55 to 2.70 ± 1.08		4.56 ± 1.55 to 4.70 ± 1.08		4.56 ± 1.55 to 2.70 ± 1.08		0.001
Alkaline phosphatase after glyceryl trinitrate use							
High	25 (83.3%)		5 (100%)		0 (0%)		0.002
low	5 (17.7%)		0 (0%)		25 (100%)		
Technical success and patient satisfaction							
Present	25 (83.3%)		0 (0%)		25 (100%)		0.001
Absent	5 (17.7%)		5 (100%)		0 (0%)		

Table 2: *Factors determine technical and clinical success of glyceryl trinitrate therapy of the studied calcular cholecystitis patients (n = 25).*

n = Total number of patients in each group; Quantitative data were expressed as mean ± SD; Qualitative data were expressed as number (percentage); •: Mann Whitney U test; ‡: Chi-square test; p-value < 0.05 is significant.

Of the 30 patients, 25 (83.3%) experienced gradual improvement of clinical, laboratory and radiological signs of CBD stone that denoted technical and clinical success. While the remaining 5 (16.7%) cases revealed elevated pancreatic enzymes which denoted failed medical management with persistence of the stone and needed ERCP then cholecystectomy later on (p = 0.001).

There was a significant differences between patients with succeeded medical treatment and patients with failed medical treatment regarding days of medical therapy (p = 0.023), size of the stone and age of the patient (p = 0.001). There was a significant reduction in Alkaline phosphatase in 25 patients (83.3%) with passed stones (p = 0.002).

Ultrasonography showed significant gradual reduction in CBD diameter (p = 0.001) during GTN treatment which denoted passage of the stone.

Operative management of patients that did not respond to GTN medical therapy

Of the included 30 patients the five patients who failed to respond to medical therapy with persistent stone and clinical evidence of starting pancreatitis underwent ERCP and cholecystectomy.

Discussion

It was found the CBD incidence in patients with symptomatic gallstones and asymptomatic gallstones was bout 10 - 20% to < 5% respectively [6]. Patients with a suspected gallbladder stones and stone in the CBD stones were clinically evaluated then underwent classic biochemical and hematologic tests which included liver function tests, pancreatic function tests and trans-abdominal ultrasound assessment [2].

Complications of CBDS include; partial or complete obstruction of the bile flow which lead to cholangitis, liver abscesses, obstructive jaundice, secondary biliary cirrhosis and pancreatitis. Such complications might occur suddenly [7]. Sometimes CBD small stones might occur in asymptomatic patients with chronic calcular cholecystitis due to spasm of SO or due to SOD. Previous studies showed that there are many patients will pass CBD stones spontaneously into the duodenum before or after laparoscopic cholecystectomy without a need to ERCP [8,9].

Active treatment of CBD stone by extracting them through ERCP is restricted to stones more than 7 mm while it is better to try conservative medical therapy in small stones which are less than 6 mm [10].

It was hypothesized that entrapped stone in the CBD might be due to SOD and the effect of medical treatment with nitrates on the SO has been investigated. It was previously found that oral nitrates to reduce SO pressure and relax its spasm [3,11]. There are no clinical trials assessed GTN use in SOD due to recorded side effects as headache, the inconvenience of long-term oral therapy, and tachyphylaxis. It remains controversial, whether using GTN medical therapy as a novel therapy could be beneficial as a non-invasive therapeutic option for management of CBD stone in SOD.

Our results showed marked success of GTN in most cases with small stone in the CBD which denoted that GTN significantly affect the SO muscle, which means avoiding unnecessary ERCP.

Similar results found by Bistritz., *et al.* [12] and Staritz., *et al* [3]. Moreover similar to us Ding., *et al.* [13] meta-analysis showed that patients who received GTN were less likely to have pancreatitis. From clinical point of view, three studies [14-16], assessing sublingual GTN administration and revealed results similar to us. The results of our research are different from findings reported by Meckeler [17]. The authors did not show GTN expected dilating effect, the conflicting results are explained. By that their study has been performed 8 days after cholecystectomy. The greatest benefits of GTN therapy was passage of small and medium sized stones in the CBD through the intact papilla [18].

Previous studies support our study that sublingual GTN has been proved to be more effective in improving post-cholecystectomy pain resulted from SOD [19].

Moreover GTN topical application could be used during ERCP as it inhibits motility of the duodenum and SO. Sublingual GTN might lead to occurrence of headache and may cause hypotension. Local administration to the papilla was not associated with systemic effects [20].

Additionally Shoji., *et al.* [21], demonstrated the effectiveness of topical GTN drip infusion for a retained CBD stone when stone size is small.

In summary, our present study showed GTN relax SO and could control SOD which entrapped small stones and could be a suitable medical alternative therapy for a CBD small stone and the sublingual route of administration GTN is recommended.

Conclusion

Small stone in the CBD might be resulted from a spasm in sphincter of oddi and could be effectively managed by medical treatment using GTN which could result in a clinical recovery of most patients and ERCP and cholecystitis could be done later on.

Bibliography

1. Dasari BVM., *et al*. "Surgical versus endoscopic treatment of bile duct stones". *Cochrane Database of Systematic Reviews* (2013).
2. Bansal VK., *et al*. "Single-stage laparoscopic common bile duct exploration and cholecystectomy versus two-stage endoscopic stone extraction followed by laparoscopic cholecystectomy for patients with concomitant gallbladder stones and common bile duct stones: a randomized controlled trial". *Surgical Endoscopy* 28 (2014): 875-885.
3. Staritz M., *et al*. "Effect of glyceryl trinitrate on the sphincter of Oddi motility and baseline pressure". *Gut* 26 (1985): 194-197.
4. Afghani E., *et al*. "Sphincter of Oddi Function and Risk Factors for Dysfunction". *Frontiers in Nutrition* 4 (2017): 1.
5. Thomas WR., *et al*. "Endoscopic retrograde cholangiography: Complications, emergencies, and related topics". *IJAM* 4.2 (2018): 124-141.
6. Williams E., *et al*. "Updated guideline on the management of common bile duct stones (CBDS)". *Gut* 66 (2017): 765-782.
7. Cox MR., *et al*. "Timing and nature of presentation of unsuspected retained common bile duct stones after laparoscopic cholecystectomy: a retrospective study". *Surgical Endoscopy* 29 (2015): 2033-2038.
8. Collins C., *et al*. "A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: natural history of choledocholithiasis revisited". *Annals of Surgery* 239 (2004): 28-33.
9. Lefemine V and Morgan RJ. "Spontaneous passage of common bile duct stones in jaundiced patients". *Hepatobiliary and Pancreatic Diseases International* 10 (2011): 209-213.
10. Möller M., *et al*. "Natural course vs interventions to clear common bile duct stones: data from the Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography". *The Journal of the American Medical Association Surgery* 149 (2014): 1008-1013.
11. Wu SD., *et al*. "Nitroester drug's effects and their antagonistic effects against morphine on human sphincter of Oddi motility". *World Journal of Gastroenterology* 11 (2005): 2319-2323.

12. Bistritz L and Bain VG. "Sphincter of Oddi dysfunction: Managing the patient with chronic biliary pain". *World Journal of Gastroenterology* 12.24 (2006): 3793-3802 .

13. Ding J., *et al*. "Glyceryl Trinitrate for Prevention of Post-ERCP Pancreatitis and Improve the Rate of Cannulation: A Meta-Analysis of Prospective, Randomized, Controlled Trials". *Plos One* 8.10 (2013): 75645.

14. Xiao-wei C., *et al*. "Nitroglycerin for prevention of post-ERCP pancreatitis and hyperamylasemia". *Chinese Journal of Digestive Endoscopy* 29 (2012): 181-184.

15. Sudhindran S., *et al*. "Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopancreatography-induced pancreatitis". *British Journal of Surgery* 88 (2001): 1178-1182.

16. Hao JY., *et al*. "Prophylactic effect of glyceryl trinitrate on post-endoscopic retrograde cholangiopancreatography pancreatitis: A randomized placebocontrolled trial". *World Journal of Gastroenterology* 15 (2009): 366-368.

17. Meckeler KJH and Borow M. "Direct manometric study of the sphincter of Oddi in man". *Gastroenterology* 68 (1975): 1038.

18. Hopton DS and Torrance HB. "Action of various analgesic drugs on the human common bile duct". *Gut* 8 (1967): 296-300.

19. Armstrong PW., *et al*. "Blood levels after sublingual nitroglycerin". *Circulation* 59 (1979): 585-588.

20. W Luman., *et al*. "Topical glyceryl trinitrate relaxes the sphincter of Oddi". *Gut* 40 (1997): 541-543.

21. Shoji M., *et al*. "Topical nitrate drip infusion using cystic duct tube for retained bile duct stone: A six patients case series". *World Journal of Gastrointestinal Surgery* 5.6 (2013): 210-215.

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