EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY OF BILIARY AND PANCREATIC STONES

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EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY OF BILIARY AND PANCREATIC STONES

EXTRACORPORELE SCHOKGOLF LITHOTRIPSIE VAN

GAL- EN PANCREASSTENEN

PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de rector magnificus

Prof. dr C.J. Rijnvos

en volgens het besluit van het college van dekanen

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To Rosine and Inne

To my parents

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CHAPTER 1

Introduction

1.1 History of gallstone disease

In about 2,000 BC, the gallbladder and bile ducts were described by the Babylonians. Trallianus, a Greek physician in the fifth century, was perhaps the first to describe calculi in the bile ducts of a human liver. Early treatment of gallstone disease consisted of water therapy. Dissolution of the stones and/or stimulation of expulsion of the stones from the gallbladder was attempted by taking "treatments" of waters rich in mineral salts, especially magnesium sulphate, in famous places like Carlsbad, Marienbad, Kissingen, Harrogate and Bath. In 1676, Joenisius described the first successful cholecystolithotomy. He removed gallstones from a biliary fistula of the abdominal wall which had formed following the bursting of an abscess. After the first general anesthetic was given in the Massachusetts General Hospital in 1846, operative pain could be more or less controlled.

The modern history of gallstone treatment started on July 15, 1867 when John S. Bobbs performed the first elective cholecystolithotomy (1,2). The Berlin surgeon Carl Langenbuch thought that leaving the gallbladder *in situ* would result in recurrence of stones. Langenbuch stated: "the gallbladder is the proper building place of the stones" and "people who perform cholecystolithotomy and cholecystostomy have busied themselves with the product of the disease, not the disease itself". After developing the technique of cholecystectomy by dissecting cadavers over several years, he performed the first cholecystectomy in man on July 5, 1882 in Berlin, Germany. The patient recovered rapidly, was smoking a cigar in bed on the first postoperative day, was ambulatory at day 12 and was discharged 6 weeks after the operation (3,4).

Thus the therapy was "settled" but one serious problem remained: how to improve the correct diagnosis of gallstone disease. Until the early 20th century, the patient's past medical history was the only diagnostic tool available to the physician. In 1924, Graham introduced a major diagnostic breakthrough, cholecystography. It was then possible to diagnose gallbladder stones in the absence of jaundice and colics by visualizing the stones radiographically. The cholecystography was the unchallenged method for the investigation of gallbladder stones for about 50 years until the introduction of ultrasound imaging in 1972. At first ultrasonography was a complementary study after a normal cholecystogram had been obtained in patients with a strong clinical suspicion of cholelithiasis. Due to refinements in instrumentation and scanning techniques the detection rate of gallbladder stones increased to more than 95%. The preference for ultrasonography is due to its high accuracy, ease of performance, lack of ionizing radiation, and ability to image the entire upper abdomen at the time of examination. Oral cholecystography became an obsolete technique (5-8).

After the development and introduction of non-surgical treatments of gallbladder stones (such as oral dissolution therapy, extracorporeal shock wave lithotripsy, and local contact dissolution (with methyl *tert*-butyl ether)) it became mandatory to obtain more information than just the presence of stones in the gallbladder (9-11). The success of these therapies depends for a great part on adequate patient selection. To achieve this it is necessary to be informed about: the number, the size and the chemical composition of the stones, the patency of the cystic duct, the absence of acute cholecystitis, cholangitis or pancreatitis, and the absence of concomitant common bile duct stones. This information can not be obtained by ultrasonography alone. Therefore oral cholecystography has regained a place in detecting calcifications of the stones and the patency of the cystic duct. Furthermore comparison between ultrasonography and oral cholecystography is advised for precise determination of the number and the size of the stones (12). Recently Brakel et al. showed that computed tomography can enable prediction of gallstone composition more precisely than plain radiography or oral cholecystography (13). Because of the high associated costs of computed tomography, and because assessment of the chemical composition of stones became less important after non-surgical gallstone therapies had widened their inclusion criteria ((partially) calcified stones now also being included), 'routine' computed tomography scans in the imaging workup of gallstones have become economically unfeasible (14-17).

1.2 Epidemiology of gallbladder stones and indications for therapy

Gallstone disease presents a major clinical problem in western society. Epidemiological studies demonstrate a prevalence of gallstones in Europe between 5 and 25% (18-21). Seventy-eighty percent of all gallstones (in western countries) are mainly composed of cholesterol (22,23). The prevalence increases with age, is higher in females, and obese people (23-26). Some ethnic populations and people in several geographic regions also have an increased risk of developing gallbladder stones. Higher prevalences (25-50%) have been detected in Mexican Americans and several Indian tribes (27-31). Reports regarding the relationship between diet and gallbladder stones are inconclusive (24,25,32). An increased incidence of gallbladder stones is found in patients with a history of childbearing (19), in patients following rapid weight reduction, probably due to increased lithogenicity of the bile (33); in patients who had total parenteral nutrition probably due to gallbladder bile stasis caused by a lack of gallbladder contractions and/or due to bile composition abnormalities due to total parenteral nutrition (34-36); in patients who had undergone estrogen therapy for prostatic cancer, probably due to changes in bile cholesterol concentration (37).

Nowadays there is, more or less, consensus that patients with asymptomatic gallbladder stones without concomitant disease do not require therapy for their stones (38-41). Gallbladder stones are considered symptomatic, according to the 'Roma 88 working team report', when patients have pain longer than 15 minutes and shorter than 12 hours, usually located in the epigastrium and/or right upper quadrant, sometimes radiating to the back, in the absence of other abnormalities which can explain these abdominal complaints (42). There may be some indications for cholecystectomy in patients with asymptomatic stones. Diabetics with asymptomatic stones have a greater risk of developing complications of stones (especially acute cholecystitis) than non-diabetics, which are associated with an increased morbidity and mortality. The results of elective cholecystectomy in diabetics are as good as in non-diabetics (41,43,44). Therefore some authors advocate preventively cholecystectomy in diabetics, especially if they are still free from cardiovascular and renal disease (45-47). Other studies, based on decision analysis models, have discounted the benefit of preventive cholecystectomy in diabetics with asymptomatic stones and concluded that there is no indication for cholecystectomy in patients, diabetics or non-diabetics, with asymptomatic gallbladder stones (48-50). Patients who will undergo transplantation surgery and immunosuppressive therapy or patients who will have life-long total parenteral nutrition may obtain benefit from preventive cholecystectomy. Sugarbaker stated that cholecystectomy should be performed at the initial operation in young patients who will receive total parenteral nutrition for a long period of time (personal communication). Cholecystectomy is also recommended in patients with a porcelain or calcified gallbladder. There is an estimated 20-60% incidence of carcinoma in these gallbladders (51-53). Patients with asymptomatic gallbladder stones first discovered at laparotomy for another cause are at particular risk of developing symptoms and complications if the stones are left *in situ* (54-57). "En passant" cholecystectomy for asymptomatic gallbladder stones does not negatively influence the results of the initial abdominal operation and prevents post-operatively cholecystitis. Some authors recommend "en passant" cholecystectomy at all abdominal operations (54,55,57-62). To our knowledge there are no reports considering the impact of laparoscopic cholecystectomy on the management of asymptomatic cholecystolithiasis.

1.3 Treatment modalities for gallstone disease

Cholecystectomy was the only treatment option for gallbladder stones for almost a century and nowadays cholecystectomy is still the gold standard. Cholecystectomy is a very effective therapy for relief of symptoms of gallbladder stone disease and carries no risk of stone recurrence. However, cholecystectomy has a morbidity rate of 5-20% and a mortality rate of 0.1-0.3% in patients younger than 70 years. These rates will rapidly increase in patients over 70 years (63). Despite the good results obtained by cholecystectomy, several alternative treatment modalities have been developed during the last decades to reduce the morbidity, the mortality, the hospital stay and the costs.

Dissolution of gallstones by orally administered bile acids (cheno and/or ursodeoxycholic acid) was first reported in 1972 and was the first non-operative therapy for gallbladder stones (9). The main importance of the introduction of oral bile acids was that it seemed possible to treat gallbladder stone disease without surgery. Problems of oral bile acid therapy were the low proportion of stones (15-25%) which were suitable for dissolution therapy, the low success rate (20-50%) total stone clearance after two years dissolution therapy), and the 10% cumulative recurrence percentage per year (64-66).

Hereafter other non-operative treatments were introduced: percutaneous cholecystolithotomy (67,68), local contact dissolution with methyl *tert*-butyl ether (MTBE) (69-71), rotary contact lithotripsy (72), and extracorporeal shock wave lithotripsy (ESWL) (10,14,73-76). The area of ESWL is the subject of this thesis.

Surgical alternatives to the 'classic' cholecystectomy were introduced more recently. O'Dwyer et al. presented their experience with the 'mini-cholecystectomy' which is a 'classic' cholecystectomy through a 5 cm subcostal incision. They stated that this 'new' surgical technique is safe, with good results, rapid recovery and short hospital stay. A real breakthrough in surgery was the introduction of laparoscopic cholecystectomy (77). Laparoscopic cholecystectomy is effective and can be performed safely (even as a day-case outpatient treatment) (78). Schirmer et al. stated that laparoscopic cholecystectomy, only 4 years after its introduction, should be considered as the treatment of choice for symptomatic cholelithiasis (79).

1.4 Extracorporeal shock wave lithotripsy of gallbladder stones

The technique of stone fragmentation by shock waves was developed in mining engineering in Russia in the 1950's (80). The use of shock waves for the destruction of kidney stones was clinically introduced in 1980 (81,82). After the good results with ESWL in the treatment of kidney stones, research was started into the possible application of ESWL for gallbladder stones. In 1983 successful laboratory tests were published and in 1986 Sauerbruch reported the first clinical results with ESWL for gallbladder and common bile duct stones (10,83). After in vitro and in vivo efficacy and safety studies were carried out in our surgical laboratory, we began using ESWL for gallbladder stones in 1989 (14,84,85). The results of this therapy in our institute are presented in chapter 2.

In contrast with ESWL for kidney stones, where residual fragments after lithotripsy can be voided via the urinary tract, spontaneous total stone clearance from the gallbladder after fragmentation cannot always be expected. This is not only due to a discrepancy between the diameter of the fragments and the diameter of the cystic duct but especially due to anatomical barriers in the biliary tract. Therefore adjuvant treatment after ESWL is necessary to achieve a total stone-free gallbladder (80,86). The combination of ESWL and oral bile acids (cheno and ursodeoxycholic acid) is the common treatment strategy in most ESWL centers (14,73,75). Oral bile acids have proved to be able to dissolve cholesterol gallstones (9). The inclusion and exclusion criteria for ESWL with oral bile acid adjuvant treatment are therefore not only dependent on patient characteristics but also on stone characteristics. Most centers use the criteria as proposed by the Munich group. Eligible patients for ESWL and adjuvant oral bile acids therapy had a history of biliary colic; a single radiolucent gallbladder stone with a diameter up to 30 mm, or up to three stones with a similar total stone mass; gallbladder visualization on oral cholecystography; no lung tissue, cysts or aneurysms in the shock wave path; no acute biliary disease; no pregnancy; and no coagulation disorders. Only cholesterol stones with small diameters were treated in the beginning with excellent results (73). About 15-25% of the patients with symptomatic gallbladder stones were suitable for ESWL using the initial inclusion criteria. Efforts to widen these inclusion criteria were undertaken but the numbers were too small to draw definite conclusions (14,15,87,88).

Another problem of this combination therapy is the long duration of the adjuvant therapy with oral bile acids and consequent high costs. ESWL followed by MTBE instillation in the gallbladder has been tried to speed up the dissolution process (16,17). This combination was only partially successful. To increase the efficacy and to evaluate the safety of simultaneous treatment with ESWL and MTBE we have performed an in vitro and in vivo animal study. The results of this experiment are presented in chapter 3.

Maybe the greatest disadvantage of ESWL and other gallbladder saving therapies is the risk of recurrence of stones (89-96). Chapter 6 contains a small review of the prevalence of recurrence after gallbladder saving therapies and research topics for the prevention of stone recurrence will be discussed.

Radiological imaging is not only important before and during ESWL but also after ESWL in the follow-up of patients. A radiology department with specialists in ultrasonography is mandatory to eliminate observer errors as much as possible. Results can be overestimated and recurrence percentages can also be overestimated by missing small particles in the gallbladder after partially successful dissolution (96,97). The value of ultrasound in the follow-up after ESWL is discussed in chapter 4.

As mentioned before, ESWL is not the only non-surgical treatment for gallbladder stones. In chapter 5, seven alternative treatment modalities (including the recently introduced laparoscopic cholecystectomy) will be discussed with the emphasis on the applicability percentages for each therapy.

1.5 Extracorporeal shock wave lithotripsy of common bile duct stones

Bile duct stones remained an unsolvable problem until January 21, 1890 when Courvoisier carried out the first successful choledochotomy for choledocholithiasis. In the early days of biliary tract surgery, morbidity and mortality rates were high, but these rapidly decreased with growing experience in surgery, anesthesia and knowledge of the coagulation cascades.

Surgery for common bile duct stones is now an accepted therapy but still has serious morbidity and mortality rates (5-8%) in the elderly or high-risk patients (63,98-100). Endoscopic stone extraction after papillotomy was introduced in 1972 and is nowadays the treatment of choice for patients with common bile duct stones with prior cholecystectomy or for high-risk operation patients. However in approximately 10% of the patients it is not possible to cannulate the sphincter of Oddi and to extract the stones from the common bile duct, due to discrepancies between the diameter of the stones and the diameter of the distal common bile duct or due to anatomical variants, either congenital or after surgery (101-103). After the successful introduction of ESWL in the treatment of kidney stones, the applicability of ESWL in the treatment of other stones became a topic of research. In 1986 Sauerbruch presented the first successful fragmentation of common bile duct stones by ESWL (10).

1.6 Extracorporeal shock wave lithotripsy of pancreatic duct stones

Another application of ESWL is in the treatment of pancreatic duct stones. About 90% of patients with chronic calcifying pancreatitis (mostly due to alcohol abuses) will develop pancreatic duct stones (104). The treatment of pancreatic duct stones is a serious clinical problem. Endoscopic stone extraction after papillotomy is (similar to common bile duct stones) the treatment of choice but is far more often impossible due to anatomical factors than in endoscopy for common bile duct stones. Most patients who cannot be treated by endoscopic extraction will require extensive surgery. The morbidity and mortality of surgery for chronic calcifying pancreatitis vary between 20-40%, and 2-5% respectively (105). After the good results with ESWL for gallbladder and common bile duct stones there was encouragement to apply ESWL in patients with pancreatic duct stones in whom endoscopic stone extraction was impossible. In 1988 the first results of ESWL for pancreatic duct stones were reported (106).

1.7 Aims of the study

The aim of the study was to answer the following questions:

- Is extracorporeal shock wave lithotripsy for gallbladder stones a safe and effective therapy? (Chapter 2)
- Is simultaneous treatment with extracorporeal shock wave lithotripsy and the solvent methyl *tert*-butyl ether feasible, safe, and more effective than either treatment alone? (Chapter 3)
- Is ultrasonography reliable for the evaluation of ESWL-results? (Chapter 4)
- What proportion of patients, with symptomatic gallbladder stones, is suitable for the current operative and non-operative treatment modalities? (Chapter 5)
- Is stone recurrence inevitable after gallbladder saving therapies? (Chapter 6)
- Is extracorporeal shock wave lithotripsy a safe and effective therapy for common bile duct stones? (Chapter 7)
- Is extracorporeal shock wave lithotripsy a safe and effective therapy for pancreatic duct stones? (Chapter 8)

1.8 References

1. Glenn F, Grafe WR. Historical events in biliary tract surgery. Arch Surg 1966; 93: 848-52.
2. Lyons AS, Petrucelli RJ eds. Medicine: an illustrated history. Abradele Press. Harry N. Abrams, Inc, Publishers, New York, 1987.
3. Langenbuch C. Ein Fall von Extirpation der Gallenblase wegen chronischer Cholelithiasis. Heilung. Berliner Klin Wochenschr 1882; 19: 725-7.
4. Traverso LW. Carl Langenbuch and the first cholecystectomy. Am J Surg 1976; 132: 81-2.
5. Hublitz UF, Kahn PC, Sell LA. Cholecystosonography: an approach to the nonvisualized gallbladder. Radiology 1972; 103: 645-9.
6. Cooperberg PL, Burhenne HJ. Real-time ultrasonography: diagnostic technique of choice in calculous gallbladder disease. N Engl J Med 1980; 302: 1277-9.
7. Simeone JF, Ferrucci JT. New trends in gallbladder imaging. JAMA 1981; 246: 380-3.
8. Cooperberg PL, Gibney RG. Imaging of the gallbladder, 1987. Radiology 1987; 163: 605-13.
9. Danzinger RG, Hofmann AF, Schoenfield LJ, Thistle JL. Dissolution of cholesterol gallstones by chenodeoxycholic acid. N Engl J Med 1972; 286: 1-8.
10. Sauerbruch T, Delius M, Paumgartner G, Holl J, Wess O, Weber W, Hepp W, Brendel W. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22.
11. Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Rapid dissolution of gallstones by methyl tert-butyl ether. NEngl J Med 1985; 312: 217-20.
12. Simeone JF, Mueller PR, Ferrucci JT. Nonsurgical therapy for gallstones: implications for imaging. AJR 1989; 152: 11-7.
13. Brakel K, Laméris JS, Nijs HGT, Terpstra OT, Steen G, Bijlenberg BC. Predicting gallstone composition with CT: in vivo and in vitro analysis. Radiology 1990; 174: 337-41.
14. Toom R den, Vergunst H, Nijs HGT, Brakel K, Laméris JS, Terpstra OT. Electromagnetic shock wave lithotripsy of gallbladder stones using a wide range of inclusion criteria. Am J Gastroenterol 1992; 87: 498-503.
15. Darzi A, El-Sayed E, O'Morain C, Tanner WA, Keane FBV. Piezoelectric lithotripsy for gallbladder: analysis of results in patients with extended selection. Br J Surg 1991; 78: 163-6.
16. Peine CJ, Petersen BT, Williams HJ, Bender CE, Patterson DE, Segura JW, Nagorney DM, Warner MA, Thistle JL. Extracorporeal shock-wave lithotripsy and methyl tert-butyl ether for partially calcified gallstones. Gastroenterology 1989; 97: 1229-35.
17. Holl J, Sauerbruch T, Sackmann M, Pauletzki J, Paumgartner G. Combined treatment of symptomatic gallbladder stones by extracorporeal shock-wave lithotripsy (ESWL) and instillation of methyl tert-butyl ether (MTBE). Dig Dis Sci 1991; 36: 1097-101.
18. The Rome group for epidemiology and prevention of cholelithiasis (GREPCO). The epidemiology of gallstone disease in Rome, Italy. Part I. Prevalence data in men. Hepatology 1988; 8: 904-6.
19. GREPCO. The epidemiology of gallstone disease in Rome, Italy. Part II. Factors associated with the disease. Hepatology 1988; 8: 907-13.
20. Barbara L, Sama C, Morselli Labate AM. A population study on the prevalence of gallstone disease: the Sirmione study. Hepatology 1987; 7: 913-7.
21. Jørgensen T. Prevalence of gallstones in a Danish population. Am J Epidemiol 1987; 126: 912-21.
22. van Erpecum KJ, van Berge Henegouwen, Stoelwinder B, Stolk MFJ, Eggink WF, Govaert WHA. Cholesterol and pigment gallstone disease: comparison of the reliability of three bile tests for differentation between the two stone types. Scand J Gastroenterol 1988; 23: 948-54.

23. Trotman BW, Soloway RD. Pigment vs cholesterol cholelithiasis: clinical and epidemiological aspects. Am J Dig Dis 1975; 20: 735-40.

24. Pixley F, Wilson D, McPherson K, Mann J. Effect of vegetarianism on development of gall-stones in women. Br Med J 1985; 291: 11-2.

25. Walker ARP, Segal I, Posner R, Shein H, Tsotetsi NG, Walker AJ. Prevalence of gallstones in elderly black women in Soweto, Johannesburg, as assessed by ultrasound. Am J Gastroenterol 1989; 84: 1383-5.

26. Jørgensen T. Gall stones in a Danish population. Relation to weight, physical activity, smoking, coffee consumption, and diabetes mellitus. Gut 1989; 30: 528-34.

27. Maurer KR, Everhart JE, Ezzati TM et al. Prevalence of gallstone disease in Hispanic populations in the United States. Gastroenterology 1989; 96: 487-92.

28. Hanis CL, Ferrell RE, Tulloch BR, Schull WJ. Gallbladder disease epidemiology in Mexican Americans in Starr County, Texas. Am J Epidemiol 1985; 122: 820-9.

29. Williams CN, Johnston JL, Weldon KLM. Prevalence of gallstones and gallbladder disease in Canadian Micmac Indian women. CAn Med Assoc 1977; 117: 758-60.

30. Thistle JL, Schoenfield LJ. Lithogenic bile among young Indian women, a high risk group for cholelithiasis. Gastroenterology 1970; 58: 1000.

31. Sampliner RE, Bennett PH, Comess LJ, Rose FA, Burch TA. Gallbladder disease in Pima Indians. Demonstration of high prevalence and early onset by cholecystography. N Engl J Med 1970; 283: 1358-64.

32. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. N Engl J Med 1989; 321: 563-9.

33. Liddle RA, Goldstein RB, Saxton J. Gallstone formation during weight-reduction dieting. Arch Intern Med 1989; 149: 1750-3.

34. Cano N, Cicero F, Ranieri F, Martin J, d'iConstanzo J. Ultrasonographic study of gallbladder motility during total parenteral nutrition. Gastroenterology 1986; 91: 313-7.

35. Messing B, Bories C, Kunstlinger F, Bernier JJ. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis. Gastroenterology 1983; 84: 1012-9.

36. Roslyn JJ, Pitt HA, Mann LL, Ament ME, DenBesten L. Gallbladder disease in patients on long-term parenteral nutrition. Gastroenterology 1983; 84: 148-54.

37. Henriksson P, Einarsson K, Eriksson A, Kelter U, Angelin B. Estrogen-induced gallstone formation in males. Relation to changes in serum and biliary lipids during hormonal treatment of prostatic carcinoma. J Clin Invest 1989; 8: 811-6.

38. Gracie WA, Ransohoff DF. The natural history of silent gallstones: the innocent gallstone is not a myth. N Engl J Med 1982; 307: 798-800.

39. Ransohoff DF, Gracie WA, Wolfenson LW. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 1983; 99: 199-204.

40. Finlayson N. Cholecystectomy for gallstones. A good thing if they cause symptoms. Br Med J 1989; 298: 133-4.

41. Gibney EJ. Asymptomatic gallstones. Br J Surg 1990; 77: 368-72.

42. Schoenfield LJ, Carulli N, Dowling RH et al. Roma 88 working team report. Gastroenterology Int 1988; 1: 17-24.

43. Rabinowitch IM. On the mortality resulting from surgical treatment of chronic gall-bladder disease in diabetes mellitus. Ann Surg 1932; 96: 70-4.

44. Eisele HE. Results of gallbladder surgery in diabetes mellitus. Ann Surg 1943; 118: 107-15.

45. Turrill FL, McCarron MM, Mikkelsen WP. Gallstones and diabetes: an ominous association. Am J Surg 1961; 102: 184-90.

46. Mundth ED. Cholecystitis and diabetes mellitus. N Engl J Med 1962; 267: 642-6.

47. Pellegrini CA. Asymptomatic gallstones. Does diabetes mellitus make a difference? Gastroenterology 1986; 91: 245-6.
48. Walsh DB, Eckhauser FE, Ramsburgh SR, Burney RB. Risk associated with diabetes mellitus in patients undergoing gallbladder surgery. Surgery 1982; 91: 254-7.
49. Sandler RS, Maule WF, Baltus ME. Factors associated with postoperative complications in diabetics after biliary tract surgery. Gastroenterology 1986; 91: 157-62.
50. Friedman LS, Roberts MS, Brett AS et al. Management of asymptomatic gallstones in the diabetic patients: a decision analysis. Ann Intern Med 1988; 109: 913-9.
51. Polk HC. Carcinoma and the calcified gallbladder. Gastroenterology 1966; 50: 582-5.
52. Berk RN, Armbuster TG, Saltzstein SL. Carcinoma in the porcelain gallbladder. Radiology 1973; 106: 29-31.
53. Fromm D. Carcinoma of the gallbladder. In Sabiston DC. ed. Textbook of surgery. Philadelphia: WB Saunders Company, 1991: 1072-5.
54. Thompson JS, Philben VJ, Hodgson PE. Operative management of incidental cholelithiasis. Am J Surg 1984; 148: 821-4.
55. Ouriel K, Ricotta JJ, Adams JT, Deweese JA. Management of cholelithiasis in patients with abdominal aortic aneurysm. Ann Surg 1983; 198: 717-9.
56. Saade C, Bernard D, Morgan S, Tasse D, Rabbat A, Nadeau N. Should cholecystectomy be done en passant for asymptomatic cholelithiasis? Can J Surg 1987; 30: 350-3.
57. Bragg LE, Thompson JS. Concomitant cholecystectomy for asymptomatic cholelithiasis. Arch Surg 1989; 124: 460-2.
58. Schreiber H, Macon WL, Pories WJ. Incidental cholecystectomy during major abdominal surgery in the elderly. Am J Surg 1978; 135: 196-8.
59. Ameli FM, Weiss M, Provan JL, Johnson KW. Safety of cholecystectomy with abdominal aortic surgery. Can J Surg 1987; 30: 170-3.
60. Biggers OR, Ready RL, Beart RW. Risk of additional intra-abdominal procedures at the time of colectomy. Dis Colon Rectum 1982; 25: 185-6.
61. Shennib H, Fried GM, Hampson LG. Does simultaneous cholecystectomy increase the risk of colonic surgery? Am J Surg 1986; 151: 266-8.
62. Thomas JH, McCroskey BL, Iliopoulos JI, Hardin CA, Hermreck AS, Pierce GE. Aortoiliac reconstruction combined with nonvascular operations. Am J Surg 1983; 146: 784-7.
63. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989; 158: 174-8.
64. Podda M, Zuin M, Battezzati PM, Ghezzi C, de Fazio C, Dioguardi ML. Efficacy and safety of a combination of chenodeoxycholic acid and ursodeoxycholic acid for gallstone dissolution: a comparison with ursodeoxycholic acid alone. Gastroenterology 1989; 96: 222-9.
65. Schoenfield LJ, Lachin JM, the Steering Committee and the National Cooperative Gallstone Study Group. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone Study. A controlled trial of efficacy and safety. Ann Int Med 1981; 95: 257-82.
66. Fromm H, Roat JW, Gonzalez V, Sarva RP, Farivar S. Comparative efficacy and side effects of ursodeoxycholic and chenodeoxycholic acids in dissolving gallstones. A double-blind controlled study. Gastroenterology 1983; 85: 1257-64.
67. Kellett MJ, Wickham JEA, Russell RCG. Percutaneous cholecystolithotomy. Br Med J 1988; 296: 453-5.
68. Chiverton SG, Inglis JA, Hudd C, Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy: the first 60 patients. Br Med J 1990; 300: 1310-2.
69. Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Rapid dissolution of gallstones by methyl tert-butyl ether. N Engl J Med 1985; 312: 217-20.

70. Thistle JL, May GR, Bender CE et al. Dissolution of cholesterol gallbladder stones by methyl tert-butyl ether administered by percutaneous transhepatic catheter. N Engl J Med 1989; 320: 633-9.
71. Leuschner U, Hellstern A, Schmidt K et al. Gallstone dissolution with methyl tert-butyl ether in 120 patients - efficacy and safety. Dig Dis Sci 1991; 36: 193-9.
72. Miller FJ, Kensey KR, Nash JE. Experimental percutaneous gallstone lithotripsy: results in swine. Radiology 1989; 170: 985-7.
73. Sackmann M, Delius M, Sauerbruch T et al. Shock-wave lithotripsy of gallbladder stones. The first 175 patients. N Engl J Med 1988; 318: 393-7.
74. Sackmann M, Pauletzki J, Sauerbruch T, Holl J, Schelling G, Paumgartner G. The Munich gallbladder lithotripsy study: results of the first 711 patients. Ann Intern Med 1991; 114: 290-6.
75. Ell C, Kerzel W, Heyder N, Becker V, Hermanek P, Domschke W. Piezo-electric lithotripsy of gallstones. Lancet 1987; ii: 1149-50.
76. Hood KA, Dowling RH, Keightley A, Dick JA, Mallinson CN. Piezo-ceramic lithotripsy of gallbladder stones: initial experience in 38 patients. Lancet 1988; i: 1322-4.
77. Dubois F, Berthelot G, Levard H. Cholécystectomie par coelioscopie. Presse Méd 1989; 18: 980-2.
78. Reddick EJ, Olsen DO. Outpatient laparoscopic laser cholecystectomy. Am J Surg 1990; 160: 485-9.
79. Schirmer BD, Edge SB, Dix J, Hyser MJ, Hanks JB, Jones RS. Laparoscopic cholecystectomy. Treatment of choice for symptomatic cholelithiasis. Ann Surg 1991; 213: 665-77.
80. Barkun ANG, Ponchon T. Extracorporeal biliary lithotripsy. Review of experimental studies and a clinical update. Ann Intern Med 1990; 112: 126-37.
81. Chaussy Ch, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980; ii: 1265-8.
82. Chaussy Ch, Schmiedt E, Jocham D, Brendel W, Forssmann B, Walther V. First clinical experience with extracorporeally induced destruction of kidney stones by shock waves. J Urol 1982; 127: 417-20.
83. Brendel W, Enders G. Shock waves for gallstones: animal studies. Lancet 1983; i: 1054.
84. Vergunst H, Terpstra OT, Schröder FH, Matura E. Assessment of shock wave pressure profiles in vitro: clinical implications. J Lithotripsy Stone Dis 1989; 1: 289-98.
85. Vergunst H, Terpstra OT, Schröder FH, Matura E. In vivo assessment of shockwave pressures: implications for biliary lithotripsy. Gastroenterology 1990; 99: 1467-74.
86. Vergunst H, Terpstra OT, Brakel K, Laméris JS, Blankenstein M van, Schröder FH. Extracorporeal shockwave lithotripsy of gallstones. Possibilities and limitations. Ann Surg 1989; 210: 565-75.
87. Meiser G, Heinerman M, Lexer G, Boeckl O. Aggressive extracorporeal shock wave lithotripsy of gall bladder stones within wider treatment criteria: fragmentation rate and early results. Gut 1992; 33: 277-81.
88. Zeman RK, Davros WJ, Goldberg JA et al. Gallstone lithotripsy: results when number of stones is excluded as a criterion for treatment. AJR 1991; 157: 747-52.
89. Villanova N, Bazzoli F, Taroni F, Frabboni R, Mazzella G, Festi D, Barbara L, Roda E. Gallstone recurrence after successful oral bile acid treatment. A 12-year follow-up study and evaluation of long-term postdissolution treatment. Gastroenterology 1989; 97: 726-31.
90. O'Donnell LDJ, Heaton KW. Recurrence and re-recurrence of gall stones after medical dissolution: a longterm follow up. Gut 1988; 29: 655-8.
91. Ruppin DC, Dowling RH. Is recurrence inevitable after gallstone dissolution by bile-acid treatment? Lancet 1982; i: 181-5.
92. Sackmann M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gallstone recurrence rate after successful shock-wave therapy. Gastroenterology 1990; 98: 392-6.

93. Scholz DG, McCullough JE, Petersen BT, Thistle JL. Gallstone recurrence following complete dissolution with oral bile acid therapy or methyl tert-butyl ether. Hepatology 1988; 8: 1372.
94. McCullough JE, Stadheim LM, Reading CC, Petersen BT, Thistle JL. Gallstone recurrence after methyl tert-butyl ether dissolution. Gastroenterology 1990; 98: A255.
95. Norrby S, Schönebeck J. Long-term results with cholecystolithotomy. Acta Chir Scand 1970; 136: 711-3.
96. Somerville KW, Rose DH, Bell GD, Ellis WR, Knapp DR. Gall-stone dissolution and recurrence: are we being misled? Br Med J 1982; 284: 1295-7.
97. Lanzini A, Jazrawi RP, Kupfer RM, Maudgal DP, Joseph AEA, Northfield TC. Gallstone recurrence after medical dissolution. An overestimated threat? J Hepatol 1986; 3: 241-6.
98. Doyle PJ, Ward-McQuaid JN, McEwen Smith A. The value of routine peroperative cholangiography - a report of 4000 cholecystectomies. Br J Surg 1982; 69: 617-9.
99. Braun L. Zum Risiko operativer Eingriffe an Gallenblase und Gallenwegen. Chirurg 1987; 58: 413-7.
100. Meijer WS. Galblaasextirpaties in Nederland; frequentie, operatieve sterfte en postoperatieve complicaties (1987-1989). Ned Tijdschr Geneeskd 1991; 135: 1688-91.
101. Cotton PB. Endoscopic management of bile duct stones; (apples and oranges). Gut 1984; 25: 587-97.
102. Johnson AG, Hosking SW. Appraisal of the management of bile duct stones. Br J Surg 1987; 74: 555-60.
103. Martin DF, Tweedle DEF. Endoscopic management of common duct stones without cholecystectomy. Br J Surg 1987; 74: 209-11.
104. Amman RW, Akovbiantz A, Largiader F, et al. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. Gastroenterology 1984; 86: 820-8.
105. Prinz RA, Greenlee HB. Pancreatic duct drainage in 100 patients with chronic pancreatitis. Ann Surg 1981; 194: 313-20.
106. Cremer M, Vandermeeren A, Delhaye M. Extracorporeal shock wave lithotripsy for pancreatic stones. Gastroenterology 1988; 94: A80.

CHAPTER 2

Electromagnetic Shock Wave Lithotripsy of Gallbladder Stones Using a Wide Range of Inclusion Criteria

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Abstract

From April 1988 till November 1990 83 patients with symptomatic gallbladder stones were treated in the University Hospital 'Dijkzigt' Rotterdam with extracorporeal shock wave lithotripsy (ESWL) followed by oral administration of bile acids (urso- and chenodeoxycholic acid). According to our inclusion criteria patients with up to 10 stones without any limit to the size of the stone(s) were accepted for treatment. On average these patients underwent 2 sessions of ESWL with an electromagnetic lithotriptor (Lithostar^R and Lithostar Plus^R, Siemens AG, Erlangen, Germany). Fragmentation of stones was achieved in 70/83 (84%) patients. The best results were achieved in patients with a solitary gallstone (50% of these patients were stone-free 12 months after ESWL). Four per cent of the patients with 2-3 stones, and 12% of the patients with 4-10 stones were free of stones 12 months after ESWL. Twenty-eight (34%) patients suffered from biliary colics after ESWL and 3 patients (3.5%) developed pancreatitis. The administration of oral bile acids was complicated by transient diarrhoea in 15 (18%) patients. ESWL followed by oral bile acid therapy is a relatively effective and safe therapy for a highly selected population of patients with gallbladder stones, which can be performed on an outpatient basis. Although the results for multiple stones were poor, the usage of wide inclusion criteria (up to 10 stones of any size) did not affect the success rate of ESWL for multiple stones.

Introduction

Gallbladder stones present a major health problem in western society. About 10% of all adults in our part of the world have gallbladder stones and this percentage increases in the elderly (1,2). Most of the gallbladder stones remain asymptomatic and do not require any treatment (3,4,5). For symptomatic gallbladder stones cholecystectomy is the gold standard. This operation has a morbidity of 10-30% and a low mortality of 0.1-0.3%. However, this increases in patients older than 70 years to 5% or more (6). Therefore several alternative non-operative treatment modalities have been recently developed. Cholesterol gallstones can be dissolved by orally or locally administered solvents. The results of oral cholelitholysis are disappointing; successful stone dissolution was achieved in only 30-50% of patients with a single small cholesterol gallstone (7). Local contact dissolution by injecting directly methyl *tert*-butyl ether into the gallbladder is more successful but serious complications (bile leakage, sedation, haemolysis and duodenitis) may occur with this more invasive treatment modality (8).

Sauerbruch et al. reported in 1986 the first results of extracorporeal shock wave lithotripsy (ESWL) in 9 patients with gallbladder stones. ESWL was restricted to patients with 1-3 radiolucent gallbladder stones with a maximum diameter of 30 mm (9). It is unclear why the number of stones was limited to three and the size of the stones to 30 mm. Using this (arbitrary) set of inclusion criteria the applicability of ESWL is very limited. Since this first report the number of patients with gallbladder stones treated with ESWL has increased tremendously.

In this paper we present our experience with ESWL, using an electromagnetic shock wave device, in 83 patients with symptomatic gallbladder stones. We widened the inclusion criteria by accepting patients with up to 10 stones without a restriction in the size or the total volume of the stones.

Patients and Methods

From April 1988 to December 1990, 542 patients with suspected gallbladder stones were registered in the outpatient clinic. After the medical history was taken and physical examination was done, determination of white blood cell count (WBC), haemoglobin, cholesterol, creatinine, bilirubin, liver enzymes and amylase level was carried out. If the patient's symptoms were suggestive of symptomatic gallstones, ultrasound examination of the upper abdomen and oral cholecystography (OCG) were carried out to evaluate the possibility of ESWL. The inclusion- and exclusion criteria we used are presented in Table 1.

inclusion criteria

symptomatic gallbladder stones (last biliary colic shorter than 2 years ago)
visualization of the gallbladder on oral cholecystography
up to 10 stones on ultrasonography, no upper limit for stone diameter
diameter of the largest stones > 5 mm on ultrasonography
radiolucent stones or small calcified rim (<2mm) on oral cholecystography)

exclusion criteria

acute biliary disease (cholecystitis, jaundice, cholangitis, pancreatitis, hepatitis or concomitant common bile duct stones)
elevated serum activity of liver enzymes (>2 times upper margin of reference values).
aneurysms or cysts in the shock wave path
coagulopathy
pregnancy

Table 1. Inclusion and exclusion criteria for extracorporeal shock wave lithotripsy of gallbladder stones.

For symptomatic gallbladder stones we used the definition of the Roma 88 Working Team Report: a patient with gallbladder stones (detected by ultrasound) who experienced pain, lasting more than 15 minutes and shorter than 12 hours, usually located in the epigastrium and/or right upper quadrant, sometimes radiating to the back, in absence of other abnormalities which can explain these abdominal complaints (10).

Of the 542 patients referred to the surgical outpatient clinic, 47 patients (9%) were not initially suitable for ESWL: 13 patients had no gallbladder stones and 34 patients preferred cholecystectomy (either the traditional or the laparoscopic procedure). Thirteen patients are still in screening procedures. Of 482 patients in whom the screening procedure was completed, 98 patients (20%) were suitable for ESWL according to our criteria. The remaining 384 patients were excluded because of (one or a combination of the following reasons): more than 10 stones: 102 (27%), non-visualization of the gallbladder at OCG: 99 (26%), calcified stones : 97 (25%), asymptomatic gallbladder stones: 91 (24%), stones smaller than 5 mm: 44 (11%), acute biliary disease: 24 (6%), other reasons: 41(11%).

Of the 98 patients who were suitable for ESWL, 83 have been treated (57 females, 26 males). Nine patients were randomized in the Rotterdam Gallstone Study (ESWL versus cholecystectomy) for cholecystectomy and 6 patients preferred a 'wait and see' strategy. The mean age of the patients who underwent ESWL was 48 years (range: 24 - 81). Forty patients (48%) had a solitary stone, 28 (34%) had 2-3 stones and 15 (18%) had 4-10 stones. The mean diameter of the largest stone was 19.1 mm (range 8-35) for solitary stones, 15.9 mm (6-33) for 2-3 stones and 14.2 mm (5-30) for 4-10 stones.

The first 30 patients were treated in-hospital and were discharged one day after ESWL. Treatment of the other 53 patients and eventually retreatments of the first 30 patients were carried out as ambulatory patients. The first 14 patients were treated with the Lithostar[R] (Siemens AG, Erlangen, Germany). This lithotriptor operates on the electromagnetic shock wave generation principle and has a fluoroscopic stone localization system. There was good visualization of the radiolucent stones after oral intake of contrast (iocetamic acid) in 12 patients. In two patients the stones were visualized after injection of contrast through direct puncture of the gallbladder when visualization with oral contrast failed.

From July 1989, 79 patients underwent ESWL with the Lithostar Plus[R] (Siemens AG, Erlangen, Germany). Ten of these patients had been treated with the Lithostar before. The Lithostar Plus is equipped with an overhead module consisting of an electromagnetic shock wave generator and an ultrasound stone localization system.

All patients received adjuvant treatment after ESWL with a combination of urso- and chenodeoxycholic acid (7-8 mg/kg body weight in one dose in the evening). The medication was started one day after ESWL. An ultrasound examination of the upper abdomen, a chest X-ray and blood tests (the same as before ESWL) were carried out one day after ESWL in the first 30 in-hospital treated patients. In the next 53 patients (with outpatient treatment) only an ultrasound examination of the upper abdomen was performed, 7-10 days after ESWL.

ESWL was considered successful if after lithotripsy all fragments were smaller than 5 mm (complete fragmentation). If fragments of 5 mm or larger were present, another ESWL session was carried out. After successful ESWL the patients had an ultrasound examination of the upper abdomen every 3 months. At the same time routine laboratory tests were carried out. When no fragments in the gallbladder could be demonstrated by ultrasonography, the adjuvant treatment with oral bile acids was continued for 3 more months and then stopped if the (verification) ultrasound again showed no fragments in the gallbladder.

Statistical analysis was performed by the Kaplan-Meier test (11). In 10 patients cholecystectomy was carried out. These patients were left out of consideration from the time of cholecystectomy ('censored' observation). A comparison of stone-free patients with initially solitary or multiple stones was carried out by the logrank test. Laboratory data were statistically evaluated by the Mann-Whitney test. Fragmentation rates were compared using a test comparing two proportions assuming a binomial distribution (12).

Results

Sixteen treatments were carried out with the Lithostar in 14 patients. All patients were treated in the prone position. The average time for one ESWL-session was 81 minutes (range 60-128) in which a mean of 3719 shock waves (range 3000-5000) at a generator output setting of 19.0 kV (maximum energy) was delivered. Five patients did not need any analgesia; the other 9 patients had intravenous analgesia and/or sedation (fentanyl, midazolam). In 10 patients (71%) there was fragmentation of the stones on ultrasound one day after ESWL. Complete fragmentation (all fragments smaller than 5 mm) was achieved in 2/10 patients. In 4 patients no fragmentation was observed. Of 12 patients in whom no fragmentation or no complete fragmentation was observed, 2 patients had a retreatment with the Lithostar and 10 patients with the Lithostar Plus.

A total of 189 treatments was carried out with the Lithostar Plus in 79 patients. Fifty treatments (26%) were performed in the supine position and 139 treatments (74%) in the left-lateral position. The average time for one ESWL-session was 62 minutes (26-210) in which 2812 shock waves (1000-4000) at a mean energy level of 7 (energy scale of 1-9) were delivered. Eight patients (12%) underwent one treatment, 28 patients (41%) had two, 23 patients (33%) had three, and 10 patients (14%) had four or more ESWL-sessions. Twenty-eight treatments (15%) were carried out without analgesia whereas in 161 treatments (85%) analgesia and/or sedation (fentanyl, midazolam) was given intravenously. In 69 patients who had their first treatment with the Lithostar Plus fragmentation was observed after initial ESWL: for patients with solitary stones equal to or smaller than 20 mm in 17/17 patients, for patients with solitary stones larger than 20 mm in 12/14 (86%) patients, for patients with 2-3 stones in 19/25 (76%) patients ($p<0.05$ vs solitary stones ≤20 mm) and for patients with >3 stones in 12/13 (92%) patients (differences between all other patients groups are statistically not significant). Complete fragmentation (all fragments smaller than 5 mm) was achieved in 8/17 (47%) for solitary stones ≤20 mm, in 2/14 (14%) for solitary stones >20 mm ($p=0.05$ vs solitary stones ≤20 mm), in 8/25 (32%) for 2-3 stones and in 5/13 (38%) for >3 stones (differences between all other patients groups are statistically not significant).

Complications. ESWL resulted in cutaneous petechiae in 11/14 patients treated with the Lithostar and in none of the patients treated with the Lithostar Plus. No abnormalities of the liver, the gallbladder and the kidneys were observed on ultrasound examination of the upper abdomen after ESWL in both groups. Twenty-eight patients (34%) (6 treated with the Lithostar, 22 treated with the Lithostar Plus) suffered from biliary colics after ESWL. These colics were in all cases successfully managed with diclofenac suppositories. Acute cholecystitis did not occur in both groups. None of the patients treated with the Lithostar had pancreatitis after ESWL whereas 3 patients (3.5%) treated with the Lithostar Plus developed a mild pancreatitis 1, 2 and 13 weeks after ESWL, respectively. The pancreatitis resolved rapidly with medical treatment in two patients. The third patient had multiple fragments in the gallbladder and common bile duct and edema of the pancreas on ultrasonography. After endoscopic papillotomy and extraction of multiple fragments from the common bile duct the general condition of the patient improved and the serum values of amylase returned to normal. This patient refused a second ESWL for a large remaining fragment in the gallbladder and underwent a cholecystectomy 6 weeks after ESWL. At operation one large (11mm) and multiple small fragments were found in the gallbladder. An intra-operative cholangiography showed no fragments in the common bile duct. The gallbladder had a normal macroscopic appearance whereas light microscopy examination demonstrated chronic cholecystitis. Nine other patients (11%) had an elective cholecystectomy for unsuccessful ESWL and persisting

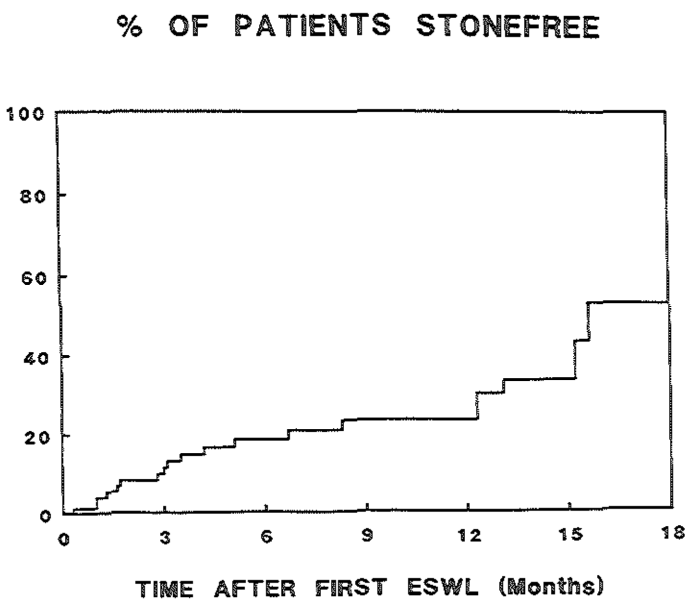

Figure 1. Results of extracorporeal shock wave lithotripsy (ESWL) in 83 patients with symptomatic gallbladder stones, counted from the first session of ESWL (n=54 at 3 months; n=39 at 6 months; n=25 at 12 months)

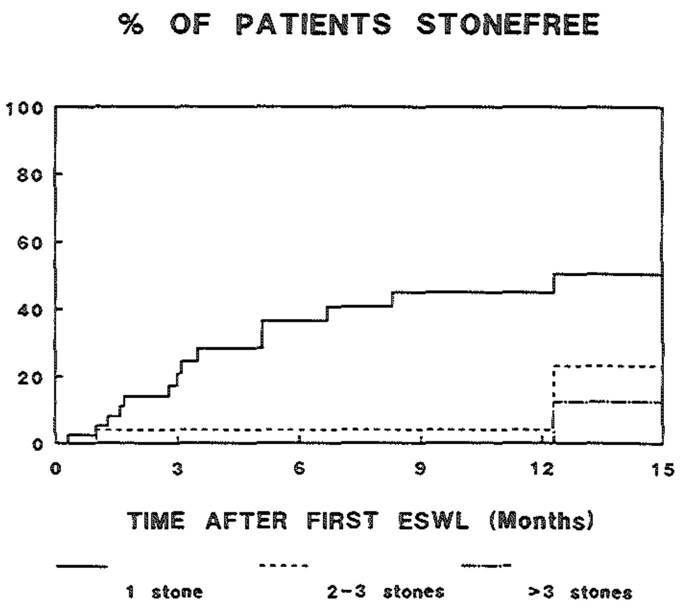

Figure 2. Results of extracorporeal shock wave lithotripsy (ESWL) in 83 patients with symptomatic gallbladder stones according to the number of stones before the first ESWL-session.

biliary colics. The mean time interval between ESWL and cholecystectomy was 9 months (range 1-22 months). In all patients there were no macroscopic pathologic changes in the gallbladder. Histological examination demonstrated chronic cholecystitis in all cases.

The adjuvant therapy with oral bile acids was complicated by diarrhoea in 15 patients (18%). After lowering the dosage of chenodeoxycholic acid in most patients the diarrhoea disappeared in a few days. Chest X-rays, 1 day after ESWL, showed no difference from images before ESWL in both groups. Blood tests after ESWL did not differ significantly from values before ESWL in both groups.

Follow-up. The median time of follow-up was 6 months (range 1-21). The percentages of patients free of stones are presented in Figure 1. Nineteen percent of the patients were free of stones 6 months after ESWL, 30% after 12 months, and 64% after 18 months. To allow comparison with results from other reports we divided the patients into three groups: solitary, 2-3 and 4-10 stones (Fig. 2). Fifty percent of all patients with solitary stones were stone-free 12-months after ESWL (for solitary stones ≤20 mm this percentage was 54% and for solitary stones >20 mm 43%, NS), whereas only 4% of the patients with 2-3 stones and 12% of the patients with 4-10 stones were stone-free (both $p<0.001$ vs solitary stones, 2-3 vs 4-10 stones NS). After 18 months 74% of the patients with solitary stones and 59% of the patients with multiple stones were free of stones.

Discussion

Extracorporeal shock wave lithotripsy (ESWL) is a relatively effective and safe therapy for a selected population of patients with gallbladder stones (13-15). The results of ESWL depend considerably on the applied inclusion criteria. Following the 'traditional' inclusion criteria as practiced by the pioneers in the field (solitary radiolucent gallbladder stone with a diameter of up to 30 mm, or up to 3 radiolucent stones with a similar total stone mass) only 25% of patients referred for lithotripsy did actually receive ESWL in Munich (16). In recent studies the inclusion criteria for stone characteristics (number, diameter, radiopaque stones) have been extended (17,18). Patients with up to 10 stones (with no limitation for the maximal diameter) and with a calcified rim on OCG (up to 2 mm) were also included for ESWL in our study. Following these inclusion criteria only 20% of the patients referred to our outpatient department for ESWL were actually suitable for ESWL. A possible explanation for this low percentage, in spite of the extension of our inclusion criteria, is the large number of patients (24%) who were excluded for asymptomatic gallbladder stones. Our percentage of patients with asymptomatic stones is much larger than in the Munich study (16). This can be due to differences in the definition of symptomatic gallbladder stones.

Three different types of shock wave generation mechanisms are used in currently commercially available lithotriptors: electrohydraulic, electromagnetic and piezoelectric devices (14). Both lithotriptors we used are working on the electromagnetic shock wave generation principle. The safety of the Lithostar as well as the Lithostar Plus has been proven in animal and clinical studies (17,19-21). There are important differences between the Lithostar and the Lithostar Plus. With the Lithostar the stones are localized by fluoroscopy whereas with the Lithostar Plus the stones are located by ultrasound. Maximum pressure delivered by the Lithostar Plus is almost twice as much as the pressure produced by the Lithostar, respectively 63.8 MPa and 32.5 MPa. The focal area (defined as the area in which at least 50% of the maximum pressure is delivered) of the Lithostar Plus is much smaller (3.5 x 40 mm) than the focal area of the Lithostar (9 x 95 mm) (22). These differences have consequences for effectiveness, potential tissue-damage and pain experienced during treatment.

The degree of stone fragmentation achieved with the Lithostar was less than with the Lithostar Plus. This can be due to the differences mentioned before between these two lithotriptors. The Lithostar Plus we used was one of the first serial produced lithotriptors of this type. This entailed that we encountered some 'teething troubles' of the lithotriptor in the beginning for which some treatment-sessions had to be stopped. These sessions were included in the analysis when more than 1,000 shock waves were delivered. Besides this we had temporary problems with the focussing mechanism such that the maximum pressure was not exactly delivered in the focal area.

In the Munich study 86% of the patients with a solitary stone equal to or smaller than 20 mm, 81% of the patients with a solitary stone of 21-30 mm and 40% of the patients with 2-3 stones were free of stones 12 months after ESWL (16). In our experience these percentages were lower: 54, 43 and 4, respectively. Other centers were also not able to reproduce the results of the Munich group (14,23,24). Interestingly, in our study the results of ESWL for 2-3 stones did not differ from the results for 4-10 stones.

It can be expected that the results of complete fragmentation by ESWL decrease when the number of stones increases. There are some explanations for this phenomenon. Firstly, correct ultrasound localization of multiple fragments is more difficult than localization of a solitary stone. Secondly, when fragmentation of the first stone occurs, a 'cloud of dust' in the gallbladder is produced which hinders optimal localization of the remaining stones. Moreover, the remaining stones can be sheltered by this 'cloud' for following shock waves. The fragments after ESWL will be larger when there is a greater total stone volume. Therefore there will be less spontaneous migration of fragments through the cystic duct and it will take longer to dissolute the fragments with oral bile acids.

Twenty-eight patients (34%) had biliary colics and 3 patients (3.5%) developed pancreatitis after ESWL. These complications were probably due to migration of fragments from the gallbladder through the cystic duct to the duodenum. Spontaneous passage of fragments is considered possible when these fragments are smaller than 5 mm (25). Adjuvant therapy with oral bile acids was given to achieve total clearance of stones in the gallbladder. The effect of adjuvant therapy is two-fold: it may dissolve the fragments after ESWL completely, and/or larger fragments can be diminished to smaller ones that may pass spontaneously through the cystic duct.

Damage of lung tissue was demonstrated in some animal studies with dogs and pigs (21,26,27). Malone et al. made a comparison of 214 chest X-rays (one day before and one day after ESWL) and could not demonstrate any pulmonary or pleural damage induced by ESWL (28). In our study we could not demonstrate any lung damage in the first 30 patients either. For that reason we abandoned the routine use of pre- and post ESWL chest X-rays.

An important drawback of ESWL and adjuvant bile acid therapy is the risk of gallstone recurrence. Follow-up in most ESWL-centers is still short, but the first results indicate that the risk of recurrence of stones after successful ESWL and oral bile acids is comparable with the risk after successful therapy with oral bile acids without ESWL: 10% cumulative per year (29,30). The percentage of patients who will get symptoms of these recurrent stones is still not clear. The usage of low dose oral bile acids or 3-hydroxy- 3 methyl-glutaryl-CoA-reductase inhibitors to prevent recurrence is still in an experimental stage. It is doubtful whether chemical ablation of the gallbladder is clinically useful to prevent gallstone recurrence (31).

We conclude that extracorporeal shock wave lithotripsy for gallbladder stones is a relatively effective and safe therapy, for a highly selected group of patients (especially patients with a solitary gallstone), which can be performed on an outpatient basis. Although the results for multiple stones are rather poor, the usage of wide inclusion criteria (up to 10 stones of any size) did not lower the overall success rate of ESWL for multiple stones. However, the precise position of ESWL in the management of patients with gallbladder stones is still unclear. To delineate the value of ESWL, randomized clinical trials, assessing the cost-effectiveness of ESWL compared with cholecystectomy as being performed in Sheffield (32) and in Rotterdam (33) are mandatory.

References

1. Pixley F. Epidemiology. In: Bateson MC, ed. Gallstone disease and its management. Lancaster, PA: MTP Press, 1986.
2. Jørgensen T. Prevalence of gallstones in a Danish population. Am J Epidemiol 1987; 126: 912-21.
3. Finlayson N. Cholecystectomy for gallstones. A good thing if they cause symptoms. Br Med J 1989; 298: 133-4.
4. Ransohoff DF, Gracie WA, Wolfenson LW. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 1983; 99: 199-204.
5. Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). Radiologic appearance of gallstones and its relationship with biliary symptoms and awareness of having gallstones. Observations during epidemiological studies. Dig. Dis. Sci 1987; 32: 349-53.
6. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989; 158: 174-8.
7. Lanzini A, Northfield TC. Review article: bile acid therapy. Aliment Pharmacol Therap 1990; 4: 1-24.
8. Thistle JL, May GR, Bender CE et al. Dissolution of cholesterol gallbladder stones by methyl tert-butyl ether administered by percutaneous transhepatic catheter. N Engl J Med 1989; 320: 633-9.
9. Sauerbruch T, Delius M, Paumgartner G et al. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22.
10. Schoenfield LJ, Carulli N, Dowling RH et al. Roma 88 working team report. Gastroenterology Int 1988; 1: 17-24.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-81.
12. Armitage R, Berry G. Statistical Methods in Medical Research. 2nd ed. Oxford, UK: Blackwell, 1987: 120-5.
13. Vergunst H, Terpstra OT, Brakel K, Laméris JS, Blankenstein M van, Schröder FH. Extracorporeal shockwave lithotripsy of gallstones. Possibilities and limitations. Ann Surg 1989; 210: 565-75.
14. Barkun ANG, Ponchon T. Extracorporeal biliary lithotripsy. Review of experimental studies and a clinical update. Ann Intern Med 1990; 112: 126-37.
15. Terpstra OT, Vergunst H, Nijs HGT, Brakel K, Laméris JS, Kate FJW ten. New aspects of extracorporeal shockwave lithotripsy of gallstones. Scand J Gastroenterol 1989; 24: 46-9.
16. Sackmann M, Delius M, Sauerbruch T et al. Shock-wave lithotripsy of gallbladder stones. The first 175 patients. N Engl J Med 1988; 318: 393-7.
17. Burhenne HJ, Becker CD, Malone DE, Rawat B, Fache JS. Biliary lithotripsy: early observations in 106 patients. Radiology 1989; 171: 363-7.
18. Peine CJ, Petersen BT, Williams HJ et al. Extracorporeal shock-wave lithotripsy and methyl tert-butyl ether for partially calcified gallstones. Gastroenterology 1989; 97: 1229-35.
19. Becker CD, Gilks CB, Burhenne HJ. Biological effects of biliary shock wave lithotripsy in swine. Invest Radiol 1989; 24: 366-70.
20. Malone DE, Becker CD, Reich KD, Quenville NF, Burhenne HJ. Soft-tissue effects of biliary extracorporeal shockwave lithotripsy in swine. Br J Radiol 1989; 62: 843-8.
21. Vergunst H, Terpstra OT, Brakel K et al. Safety and efficacy in biliary lithotripsy. In: Burhenne HJ, Paumgartner G, Ferrucci JT eds. Biliary Lithotripsy II. Chicago: Year Book Medical Publishers, Inc. 1989: 25-8.
22. Vergunst H, Terpstra OT, Schröder FH, Matura E. Assessment of shock wave pressure profiles in vitro: clinical implications. J Lithotripsy Stone Dis 1989; 1: 289-98.
23. Stamoll DA, Tagliente G, Gordon SJ. Clinical observations in shock wave lithotripsy of the gallbladder using an ultrasound-guided spark gap machine. Gastroenterology 1990; 98: A263.
24. Schoenfield LJ, Berci G, Carnovale RL, et al. The effect of ursodiol on the efficacy and safety of extracorporeal shock-wave lithotripsy of gallstones. N Engl J Med 1990; 323: 1239-45.
25. Greiner L, Münks C, Heil W, Jakobeit C. Gallbladder stone fragments in feces after biliary extracorporeal shock-wave lithotripsy. Gastroenterology 1990; 98: 1620-4.

26. Brendel W, Enders G. Shock waves for gallstones: animal studies. Lancet 1983; i: 1054.

27. Delius M, Enders G, Heine G, Stark J, Remberger K, Brendel W. Biological effects of shock waves: lung hemorhage by shock waves in dogs-pressure dependence. Ultrasound Med Biol 1987; 13: 61-7.

28. Malone DE, Becker CD, Müller NL, Burhenne HJ. Is routine chest radiography required with biliary lithotripsy? AJR; 152: 987-9.

29. O'Donnell LDJ, Heaton KW. Recurrence and re-recurrence of gall stones after medical dissolution: a longterm follow up. Gut 1988; 29: 655-8.

30. Sackmann M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gallstone recurrence rate after successful shock-wave therapy. Gastroenterology 1990; 98: 392-6.

31. Becker CD, Quenville NF, Burhenne HJ. Long-term occlusion of the porcine cystic duct by means of endoluminal radio-frequency electrocoagulation. Radiology 1988; 167: 63-8.

32. Milner PC, Nicholl J, Westlake L et al. The design of a randomized controlled trial for the evaluation of lithotripsy as a treatment for gallstones. J Lithotripsy Stone Dis 1989; 1: 122-32.

33. Nijs HGT, Toom R den, Berger MY, Lubsen J, Terpstra OT. Extracorporeal shockwave lithotripsy versus cholecystectomy: the need for randomised clinical trials. J Lithotripsy Stone Dis 1991; 3: 112-3.

CHAPTER 3

Treatment of Gallbladder Stones with Simultaneously Extracorporeal Shock Wave Lithotripsy and Contact Dissolution with Methyl Tert-Butyl Ether. An in Vitro and in Vivo Animal Study

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Abstract

RATIONALE AND OBJECTIVES: To assess in vitro and in vivo the feasibility and the safety of synchronous treatment with extracorporeal shock wave lithotripsy (ESWL) and methyl *tert*-butyl ether (MTBE) for gallbladder stones.

METHODS: In vitro: 18 stones (>90% cholesterol) from 3 surgically resected gallbladders were randomly allocated to three treatment regimens: 15 mL MTBE + 1,500 shock waves (SW) (group A); 15 mL saline + 1,500 SW (group B); 15 mL MTBE without SW. Shock waves were delivered with the Lithostar Plus[R] (Siemens AG, Erlangen, Germany) at maximum power setting.

Animal study: six human gallstones (>90% cholesterol) obtained at cholecystectomy were implanted into the gallbladders of Yorkshire pigs. Three weeks postoperatively, the gallbladder was transhepatically punctured whereafter a 6-Fr pigtail catheter was implanted. After instillation of MTBE, 1,500 SW were delivered. Pigs were sacrificed one week after treatment: stone fragmentation, macroscopic and microscopic alterations were scored. These findings were compared with the results from a previous study in which pigs (n=7) were treated with only ESWL and pigs (n=4) which only underwent the stone implantation in the gallbladder.

RESULTS: In vitro: A: 4/5 stones dissolved completely whereas 90 fragments <3 mm remained of the fifth stone. B: In 1/5 stones fragmentation failed, 4/5 stones gave 0-1000 fragments <3 mm and 1-6 fragments >3 mm. C: 5/5 stones were completely intact without reduction in diameter.

Animal study: we encountered difficulties in precise ultrasound localization of the stones after instillation of MTBE. Macroscopic autopsy findings demonstrated stone fragmentation in only 1/6 pigs; weight reduction in 5/6 stones (mean 7%, N.S.); hemorrhagic gallbladder wall 2/6; local erosion of the gallbladder epithelium 5/6 ($p < 0.05$ vs. ESWL; $p < 0.01$ vs. control); subcapsular hepatic hemorrhage 2/6; cystic duct stone 1/6; pulmonary hemorrhage 1/6. Microscopic findings showed more hemorrhagic necrosis (3/6) and scarring (2/6) of the liver and more hemorrhage of the hepatic capsule (4/6) in the ESWL + MTBE group. Laboratory values before and after treatment showed no significant changes.

CONCLUSIONS: Synchronous treatment with ESWL and MTBE was very effective in stone dissolution in vitro. The results in the animal study were disappointing, probably due to the inadequate ultrasonographic stone localization after MTBE instillation in the gallbladder. The combination therapy showed no extra tissue damage compared to monotherapy with ESWL or MTBE. Improvement of stone localization is necessary to evaluate the role of this potentially very effective combination therapy in the treatment of gallbladder stones.

Introduction

Until recently cholecystectomy was the standard treatment for most patients with symptomatic gallbladder stones. Although cholecystectomy is an effective treatment for symptomatic gallbladder stones, there exists a (low) morbidity and mortality. Therefore several operative and non-operative alternative treatments have been developed the last decade (1-10).

Extracorporeal Shock Wave Lithotripsy (ESWL) with adjuvant treatment with orally distributed bile acids was clinically introduced in 1986 and, after the initially very good results, was considered as a promising non-operative treatment for symptomatic gallbladder stones (11). After world-wide application of ESWL some major problems were encountered. Firstly, only a small percentage (20-25%) of patients with symptomatic gallbladder stones are suitable for ESWL due to narrow inclusion criteria (4,12-15). Secondly, spontaneous total clearance of the gallbladder after fragmentation of the stone(s) cannot always be expected due to anatomical barriers and due to discrepancies between the diameter of the fragments after lithotripsy and the diameter of the cystic duct. Therefore ESWL needs an adjuvant treatment to achieve total stone clearance from the gallbladder (4,16,17). The most common adjuvant treatment is the combination of orally administered urso and chenodeoxycholic acid. This adjuvant therapy implies that only cholesterol stones or stones with minimal calcifications can be treated. This dissolution therapy lasts on average for more than one year which makes this treatment an expensive one (costs about $200/month in the Netherlands (12). Thirdly, there is a risk of recurrence of stones (15% after 2 years), especially when very small fragments (not detectable or missed on ultrasound) remain in the gallbladder. These fragments can act as a nidus for new stone formation (18-20).

Local contact dissolution of gallbladder stones with methyl *tert*-butyl ether (MTBE) is another potential alternative to cholecystectomy (5,6,21). MTBE is structurally related to diethyl ether but MTBE has a boiling point of $55.2^{0}C$ and is therefore liquid at body temperature (22). MTBE can be instilled in the gallbladder or the common bile duct by a percutaneous transhepatic catheter or by an endoscopically placed nasobiliary tube. Dissolution therapy with MTBE has also restrictions concerning the inclusion criteria of patients for treatment (30-40%). The long duration of this therapy (up to several days by huge stone load) and the necessity of adjuvant treatment with oral bile acids are two other disadvantages of MTBE treatment. The risk of stone recurrence after successful MTBE therapy is 15% after 9 months, increasing to 40% after 2 years (23,24).

To increase the efficacy several non-operative therapies have been combined: MTBE-instillation after fragmentation by dye-laser (25), MTBE-instillation combined with sonication by ultrasound (26-28), ESWL synchronously with different solvents (ethyl-propionate, isopropyl-acetate and MTBE) (29).

ESWL and subsequent instillation of MTBE in the treatment of cholesterol and partially calcified gallbladder stones has been tried in animal studies and in small uncontrolled patient studies (30-32). This combination therapy could probably enlarge the percentage of suitable patients by making it possible to treat larger, multiple, and (partially) calcified stones. Moreover the success rate might be increased, the total treatment time decreased with consequent reduction in the costs of treatment.

After the good clinical results with both ESWL and MTBE as monotherapy and the promising results of ESWL followed by instillation of MTBE we were encouraged to combine these two therapies simultaneously to evaluate the feasibility, the efficacy and the safety in an in vitro and in vivo animal study.

Material and Methods

In vitro

Three sets of 6 gallbladder stones were obtained from 3 surgically resected human gallbladders, each set derived from a single patient. The mean diameter of the stones was 11 mm (range 7-14). The diameters of the stones in the three different groups did not differ significantly. One stone of each set was used for chemical analysis of cholesterol content as described earlier (33). All 3 biochemically analyzed stones consisted of more than 90% (range 90-98) cholesterol. Because all stones in one set came from one patient, we assumed that these stones had the same chemical composition as the chemically analyzed stone (34). All ESWL treatments were carried out with the Lithostar Plus^R (Siemens AG, Erlangen, Germany) which is a lithotriptor with an electromagnetic shock wave device and has an ultrasound guided localization system. With this lithotriptor shock waves with a maximum positive focal pressure of about 65 MPa (in vitro) can be generated. Pressures in vivo are 15-25% lower. The focal zone of the Lithostar Plus^R (in which at least 50% of the energy is released) has a length of 40 mm and a width of 3 mm in vitro and in vivo (35,36). The stones were placed in 50 mL polypropylene tubes (Greiner Labortechnik, Frickenhausen, Germany) and transferred to a water container which was coupled to the water cushion of the Lithostar Plus^R. (Fig. 1).

Five stones were placed in 5 tubes containing 10 mL MTBE (Merck-Schuchardt, Schuchardt, Germany) and, after localization of the stones in the shock wave focal zone, 1,500 shock waves (energy level 9=maximum power setting) were delivered (group A). Five stones were placed in 5 tubes containing 10 mL saline and, 1,500 shock waves (energy level 9) were delivered (group B). The last five stones were placed in 5 tubes containing 10 mL MTBE for 15 minutes (which was the time to deliver 1,500 shock waves) and no shock waves were given. After each treatment the number of residual fragments was counted and the diameter of fragments were measured.

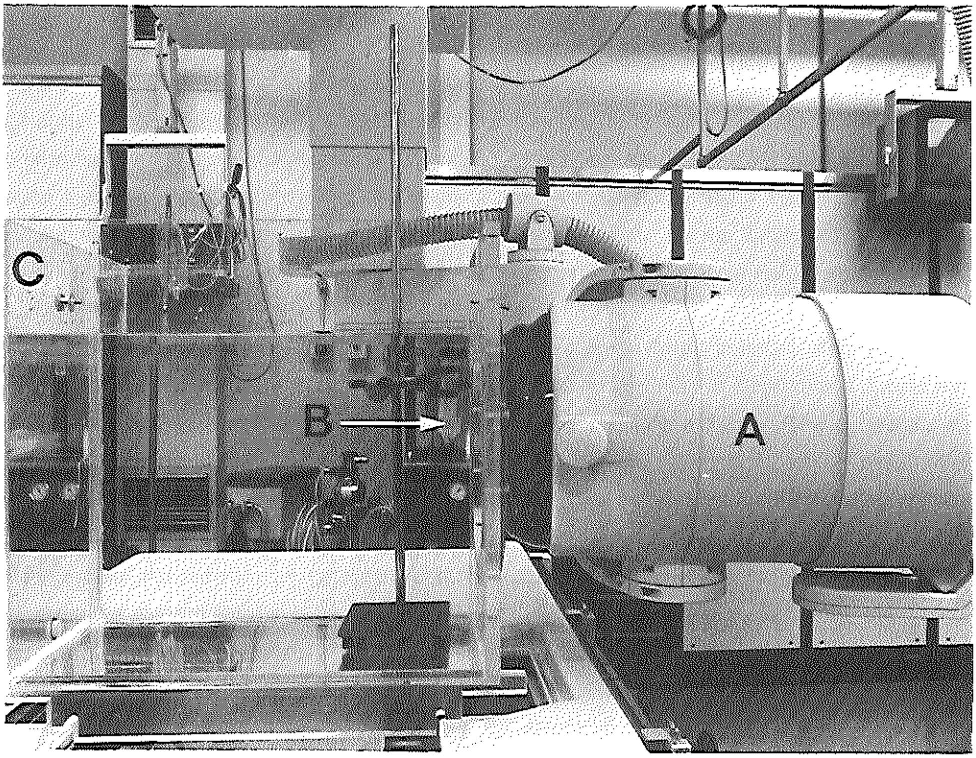

Figure 1. In vitro model for combination treatment with ESWL and MTBE. A = electromagnetic shock wave generator (Lithostar Plus[R], Siemens AG, Erlangen, Germany). B = test tube containing one gallstone, filled with either 15 mL saline or MTBE. C = water container coupled to water cushion of the Lithostar Plus[R]

Animal study

Six Yorkshire pigs (mean body weight 27 kg, range 25.5-28 kg) were used. Seven cholesterol gallstones were obtained at cholecystectomy in one patient. The mean diameter of the stones was 16 mm (range 13-19) and the mean weight of the stones was 612 mg (range 308-1192). One stone was used for chemical analysis as mentioned above. This stone consisted for more than 90% of cholesterol. The other six stones were implanted at laparotomy into the gallbladder of the pigs. Three weeks after implantation of the stones, after a two-days fast, an ultrasound guided transhepatic puncture of the gallbladder (22-gauge needle), preferably in its upper third, was carried out under general anesthesia. After insertion of a guide wire, the needle was removed and a 6-Fr polyethylene pigtail catheter (William Cook Europe A/S, Bjaeverskov, Denmark) was placed. No antibiotics were given before or during the treatment. The position of the catheter was confirmed by aspiration of bile.

After confirmation, contrast material (Telebrix, Guerbet, Aulnay S/Bois, France) was injected into the gallbladder until it entered the cystic duct to assess the overflow volume by fluoroscopy. The volume of MTBE we used was 2 mL less than the overflow volume to prevent overflow of MTBE into the bile ducts and the duodenum. After MTBE was instilled in the gallbladder the pigs were transferred to the Lithostar Plus[R] and the stones were localized by ultrasound. When the stone was in the focal zone of the lithotriptor 1,500 shock waves (energy level 9, maximum power setting) were delivered under continuous ultrasound control. After lithotripsy, MTBE was aspirated from the gallbladder. All aspirated material was placed on a blotting paper and the residue was weighed.

Laboratory tests included white blood cell count (WBC), erythrocyte count, thrombocyte count, hematocrit, serum levels of hemoglobin, total bilirubin, ureum, creatinine, activity of aspartate-amino-transferase (ASAT), alkaline phosphatase, gamma-glutamyl transpeptidase, and amylase were determined before implantation of the gallstone, on the day of the experiment (before and immediately after ESWL), and before autopsy. One week after lithotripsy the pigs were sacrificed.

At autopsy the organs of the chest and abdomen were inspected for macroscopic lesions. Both lungs were inflated with air (to differentiate superficial hemorrhages from post mortem blood stasis) before resection, thereafter with 10% buffered formalin. The liver, gallbladder, common bile duct duodenum and a part of the pancreas were resected en bloc. The efficacy of ESWL and MTBE combination therapy was assessed by measuring the total weight and maximum diameters of the recovered fragments. Tissue specimens were taken for microscopy from designated areas of the aforementioned organs and also of the upper pole of the right kidney.

To achieve a qualitative analysis of local tissue injury, the specimens of the gallbladder, liver, extrahepatic bile ducts pancreatic lymphnodes, and duodenum were scored as discrete variables (absent/present) for various microscopic tissue damage parameters. To compare the microscopic tissue damage of the pigs treated with ESWL and MTBE we have used the data of 7 pigs treated only with ESWL (4,000 or 8,000 shock waves) and 4 control pigs without any treatment but with stone implantation in the gallbladder from a previous study on tissue damage performed in our surgical laboratory (37). For the individual organs, the positive scores (presence of tissue change) were summed and divided by the total number of possible scores to calculate cumulative tissue damage indices. Similarly, an overall cumulative tissue damage index was calculated for each treatment regimen separately. To compare the tissue damage in the three groups, ratios of the cumulative tissue damage indices were calculated. A ratio of 1.0 stands for equal damage, a value > 1.0 indicates a proportional increase, a value of < 1.0 denotes a proportional decrease of tissue damage.

Statistical evaluation of the laboratory data was performed using the paired t-test. Autopsy findings and histological data were compared with the Chi-square test. Statistical significance was considered at a p-value of less than 0.05.
The study protocol was approved by the Committee on Animal Research of the Erasmus University Rotterdam.

Results

In vitro:
In group A (MTBE + ESWL) 4 of the 5 stones dissolved completely without any grit left, 90 fragments smaller than 3 mm remained of the fifth stone. In group B (ESWL + saline) fragmentation failed of one stone. The other 4 stones were fragmented with more than 100 fragments <3 mm and 1-6 fragments $\geq$3mm left. The stones in group C (MTBE) were completely intact, without reduction in diameter.

Autopsy findings	ESWL + MTBE (n=6)	ESWL (n=7)	control (n=4)
petechiae at shock wave entry site	-	-	-
intraperitoneal bile leakage	-	-	-
intra-abdominal adhesions	6	7	4
hemorrhage of the gallbladder wall	2	3	-
subcapsular hepatic hemorrhage	2	3	-
local erosion of the gallbladder epithelium	5*,**	2	-
hemorrhagic pancreatic lymphnodes	-	-	-
hematoma in omentum	-	-	-
stone fragment in cystic duct	1	1	-
pulmonary hemorrhage	0	2	-
pulmonary abscesses	-	-	-

Table 1. Autopsy findings in 6 pigs after synchronous treatment with ESWL and MTBE for a surgically implanted human gallbladder stones, compared with findings from a previous pig study (mono-therapy with ESWL; only stone implantation without treatment) (37).
* $p < 0.05$ ESWL + MTBE vs. ESWL; ** $p < 0.01$ ESWL + MTBE vs. control

In vivo:

After instillation of a mean of 10.7 mL MTBE (range 5-19 mL) in the gallbladder it was impossible to achieve a precise visualization of the gallstones by ultrasound and thus to focus the lithotriptor generator. Therefore when the most optimal localization was achieved 1,500 shock waves were delivered with regular relocalizations under continuous ultrasonographic control. The mean treatment time was 63 minutes (range 45 - 90). During the ESWL treatment fragmentation of the stones was detected in only one pig. This finding was confirmed at post treatment ultrasound but optimal visualization was again not achieved. One week after treatment visualization of the gallbladder and the stones was much better.

Laboratory values showed a slight decrease in alkaline phosphatase (mean 178 U/L vs. 165 U/L: $p < 0.05$), gamma-glutamyl transpeptidase (76 U/L vs. 52 U/L: $p < 0.05$), and amylase (2615 vs. 2314 U/L: $p < 0.05$) immediately after treatment. All values returned to pre treatment values after one week.

Autopsy findings (also of the 2 control groups) are presented in Table 1. There was a small pulmonary hemorrhage in the lower lobes of both lungs in one pig. All pigs had intra-abdominal adhesions, probably caused by the surgical stone implantation. Examination of the gallbladder showed that there were local epithelial erosions in 5/6 pigs ($p < 0.05$ vs. the ESWL group and $p < 0.01$ vs. the control group). In two pigs there was a hemorrhagic gallbladder wall. The liver showed a fibrotic beam at the place where the shockwaves entered in 2 pigs. Fragmentation of the stone was seen in one pig. This stone, with a initial diameter of 18 mm was fragmented in 4 parts of 10, 10, 8, and 9 mm. One of these fragments was impacted in the cystic duct. The other 5 stones were completely intact in the gallbladder lumen. However there was a weight reduction in the stones (mean 7%, range 1-13) but this reduction did not reach statistical significance. The duodenum, pancreas, and right kidney showed no gross abnormalities.

The absolute numbers of positive scores of microscopic tissue parameters are depicted in Table 2 (also of the 2 control groups). Mild atelectasis of the lower lobe was found in all pigs, but this finding did not appear to be clinically relevant. All gallbladders had epithelial desquamation (with necrosis in 2 gallbladders) and signs of chronic cholecystitis. The livers of 3 pigs showed small focal hemorrhagic necrosis, adjacent to the gallbladder ($p < 0.05$ vs. ESWL-group). Scarring of liver tissue was observed in 2 pigs, whereas this was found in all pigs of the ESWL-group ($p < 0.01$). Hemorrhage of the hepatic capsule was seen in 4 pigs ($p < 0.05$ vs. control-group). All other microscopic results were not statistically significantly different from the other two groups. The ratios of cumulative tissue damage indices are presented in Table 3. Both the individual organ and the overall ratios of cumulative tissue damage indices of the 3 groups did not differ significantly.

Local microscopy findings	ESWL + MTBE (n=6)	ESWL (n=7)	control (n=4)
Gallbladder			
hemorrhage of the gallbladder wall	2	4	-
epithelial degeneration / desquamation	6	6	2
cholecystitis	6	7	4
Liver			
hemorrhagic necrosis	3*	-	-
scarring	2**	7¶	-
hydropic hepatocytic degeneration	4	1§	3
inflammation	1	2	1
vasculitis	-	-	-
thrombosis	-	1	-
degeneration / desquamation of epithelium of minor biliary ducts	1	1	1
cholangitis of minor biliary ducts	-	1	1
hemorrhage of the hepatic capsule	4¥	2	-
thickening of the hepatic capsule	4	4	3
Extrahepatic bile ducts			
epithelial degeneration / desquamation	6	7	4
cholangitis	1	1	1
Pancreatic lymph nodes			
hemorrhage	-	2	-
ferrous deposition	2	4	1
sinus histiocytosis	6	7	4
cellular degeneration	-	1	1
fibrosis	-	1	1
Duodenum			
epithelial degeneration / desquamation	5	5	3
mucosal inflammation	-	1	-
inflammation of the papilla of Vater	-	-	1

Table 2. Histological findings in 6 pigs after synchronous treatment with ESWL and MTBE for surgically implanted human gallbladder stones compared with findings from a previous pig study (mono-therapy with ESWL; only stone implantation without treatment) (37).

* $p < 0.05$ ESWL + MTBE vs. ESWL; ** $p < 0.01$ ESWL + MTBE vs. ESWL;

¶ $p < 0.01$ ESWL vs. control; § $p < 0.05$ ESWL vs. control;

¥ $p < 0.05$ ESWL + MTBE vs. control.

	Ratio of cumulative tissue damage indices		
	I vs. II	I vs. III	II vs. III
gallbladder	0.96	1.56	1.62
liver	1.17	1.41	1.21
extrahepatic bile ducts	1.02	0.93	0.91
pancreatic lymphnodes	0.62	0.76	1.22
duodenum	0.97	0.83	0.86
overall	0.95	1.14	1.20

Table 3. Ratios of cumulative tissue damage indices of the three different treatment groups.
I = ESWL + MTBE (n=6); II = ESWL (n=7); III = control (n=4). Group II and III were derived from a previous study (37). All values not statistically significant.

Discussion

The introduction of laparoscopic cholecystectomy has dramatically changed the opinion of both the physician and the patient of what is the best treatment for gallbladder stones (8,9). Five year after its introduction laparoscopic cholecystectomy is already considered as the new gold standard for treating gallbladder stones with exception of the elderly, the high risk operation patients or when patients refuse surgery as a therapeutical option (38,39). For this population non surgical alternatives can be considered.

Extracorporeal shock wave lithotripsy (ESWL) and local contact dissolution with methyl *tert*-butyl ether (MTBE) are two recently introduced non-surgical treatment modalities for patients with gallbladder stones (11,21). Good results in larger series were published but also some disadvantages were recognized (5,6,40). The percentage of patients suitable for these therapies is low (ESWL: 20-25%; MTBE: 30-40%) due to the narrow inclusion criteria. Another disadvantage of ESWL and MTBE treatment is that in most cases residual fragments or grit will remain in the gallbladder. Therefore, it is necessary to give adjuvant treatment after ESWL or MTBE (5,16,17) to dissolve the small fragments in the gallbladder or to diminish the large fragments in diameter so they can pass through the cystic duct (4-6,12,40,41). Risk of recurrence of stones is a disadvantage of all gallbladder saving therapies. The recurrence rate two years after ESWL and oral bile acid treatment was 15% (18), whereas after MTBE treatment this percentage is 15% after nine months increasing up to 40% after two years (23,24).

Non-surgical treatment of gallbladder stones is especially suitable for elderly patients who have an increased risk for surgery. However, in the elderly the incidence of pigment stones is higher than in the general population (42,43). For both ESWL and MTBE pigment stones are an exclusion criterion. Therefore, these people are not the most suitable candidates for ESWL or MTBE.

Combining ESWL with local contact dissolution with MTBE after stone fragmentation might be a worthwhile non-surgical therapy for gallbladder stones. The dissolution rate of the remaining fragments after ESWL would probably be increased and consequently the post-ESWL fragment related complications could be decreased. Therefore, treatment of patients with larger stone burdens or calcified or pigmented stones might become possible.

ESWL followed by MTBE on the same day has been described in vitro and in vivo (30-32). The preliminary results seem to be better than with each therapy separately. To our knowledge there is only one in vitro study of simultaneous treatment with ESWL and MTBE and two other solvents (ethylpropionate and isopropyl-acetate). In this study only ESWL and ethylpropionate resulted in a faster dissolution (29). The aim of this study was to investigate the feasibility, the efficacy, and the safety of simultaneous treatment with ESWL and MTBE in vitro and in vivo.

We started an in vitro experiment in which 3 groups of cholesterol stones were treated with either ESWL alone, MTBE alone or a combination of the former two. The results were very promising: in the combination group in 4 out of 5 stones there was no residue, sludge or grit after 1,500 shock waves in 10 mL MTBE (15 minutes treatment time), in both the other groups there were many fragments (ESWL) or no disintegration of the stones (MTBE). One of the important points in the treatment with MTBE is the contact of MTBE with the stone surface. Applying shock waves to the stone in MTBE probably generates two stimulators for increased disintegration generated. Increasing the contact time because the stone is whirling in the liquid MTBE by the energy of the shock waves and the contact surface will be enlarged by fragmentation of the stone and by creating microfractures in the stone allowing access of MTBE.

Encouraged by these promising results we began an animal (swine) study. Although all experiments were carried out by an experienced multidisciplinary biliary lithotripsy team we were not able to achieve a precise localization of the stone in the focal zone of the lithotriptor directly after MTBE instillation in the gallbladder. We could not find an adequate explanation for this phenomenon. In vitro we had had no problems with ultrasonographic stone localization in the MTBE-group. Perhaps small hemorrhages at the puncture site or the introduction of small air bubbles during catheter placement and during the assessment of the overflow volume can be disturbing factors in the localization. The bad localization is probably the explanation for the low fragmentation and dissolution results in the animal study. Stone fragmentation was only achieved in one pig.

Localization might be improved using the recently presented endoscopic retrograde cannulation of the gallbladder and instillation of MTBE via a cysto-nasal catheter (44). With this method there are less hemorrhages and less introduction of air in the gallbladder. To our knowledge there are no reports concerning combination treatments of ESWL and MTBE in this way. Although this part of the study was not successful we have obtained information about the tissue damage after simultaneous treatment with ESWL and MTBE.

Laboratory values did not significantly differ before and after treatment. We have not measured serum MTBE-levels during or after treatment. Another study of sequential ESWL and MTBE has shown that systemic absorption of MTBE was not increased after ESWL (45). A small clinical study in 8 patients has confirmed this (32).

At autopsy all pigs showed intra-abdominal adhesions due to implantation of the stones in the gallbladder. The pulmonary hemorrhage was probably due to stone targeting through lung tissue. This phenomenon is more likely to occur in pigs than in man because of the strong caudal extension of the pleural sinus in the pig. The only difference we found in comparison with the two control groups was erosion of gallbladder epithelium. This effect is probably due to MTBE instillation. McGahan et al. also found erosion of the gallbladder after MTBE instillation (46).
Microscopic findings showed more hemorrhagic necrosis in the liver and more hemorrhage of the hepatic capsule in the ESWL and MTBE group. However, the ratios of cumulative tissue damage indices did not differ between our ESWL + MTBE, ESWL alone and control group. Studies in large animals treated by monotherapy with MTBE showed only mild inflammatory changes of the gallbladder (46,47). Adam et al. found necrosis of the gallbladder, the common bile duct, and the extrahepatic ducts in rabbits after MTBE instillation in the gallbladder (48). Van Sonnenberg et al. investigated the gallbladders after cholecystectomy of five patients who were initially treated with contact dissolution with MTBE. Chronic cholecystitis was observed in each gallbladder. Mild acute inflammatory changes were noted in two patients who underwent cholecystectomy one week after MTBE treatment. Van Sonnenberg stated that local contact dissolution with MTBE is a safe therapy and that the mild acute changes may be transient (49). Animal studies (dogs) by the Mayo-group showed no extra tissue damage of sequential treatment with ESWL and MTBE compared with monotherapy with MTBE (45,50,51). On the contrary, Vergunst et al. found significantly more epithelial degeneration of the gallbladder in pigs treated with ESWL and subsequently MTBE instillation compared with pigs only treated by ESWL. The additional tissue damage was confined primarily to the gallbladder and gallbladder bed (30).

We conclude that by combining ESWL and MTBE the results of each separate therapy can be improved in vitro. The fragmentation results in vivo were worse, probably due to inadequate stone localization by ultrasound after puncture of the gallbladder and instillation of MTBE. The combination treatment with ESWL and MTBE is a safe therapy causing no extra tissue damage, compared to monotherapy with ESWL or MTBE. Because the results of sequential treatment in vivo and our results in vivo seems more efficient than the results of either therapy alone we think that it is warranted to evaluate other techniques of localization of the stones or instillation of MTBE to assess the role of this promising and safe combination therapy of Extracorporeal Shock Wave Lithotripsy and Methyl Tert-Butyl Ether in the modern treatment of gallbladder stone disease.

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References

1. Danzinger RG, Hofmann AF, Schoenfield LJ, Thistle JL. Dissolution of cholesterol gallstones by chenodeoxycholic acid. N Engl J Med 1972; 286: 1-8.
2. Podda M, Zuin M, Battezzati PM, Ghezzi C, de Fazio C, Dioguardi ML. Efficacy and safety of a combination of chenodeoxycholic acid and ursodeoxycholic acid for gallstone dissolution: a comparison with ursodeoxycholic acid alone. Gastroenterology 1989; 96: 222-9.
3. Schoenfield LJ, Lachin JM, the Steering Committee and the National Cooperative Gallstone Study Group. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone Study. A controlled trial of efficacy and safety. Ann Int Med 1981; 95: 257-82.
4. Sackmann M, Delius M, Sauerbruch T et al. Shock-wave lithotripsy of gallbladder stones. The first 175 patients. N Engl J Med 1988; 318: 393-7.
5. Thistle JL, May GR, Bender CE et al. Dissolution of cholesterol gallbladder stones by methyl tert-butyl ether administered by percutaneous transhepatic catheter. N Engl J Med 1989; 320: 633-9.
6. Leuschner U, Hellstern A, Schmidt K et al. Gallstone dissolution with methyl tert-butyl ether in 120 patients - efficacy and safety. Dig Dis Sci 1991; 36: 193-9.
7. Chiverton Sg, Inglis JA, Hudd C, Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy: the first 60 patients. Br Med J 1990; 300: 1310-2.
8. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. Preliminary report of 36 cases. Ann Surg 1990; 211: 60-2.
9. The Southerns Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991; 324: 1073-8.
10. Miller FJ, Kensey KR, Nash JE. Experimental percutaneous gallstone lithotripsy: results in swine. Radiology 1989; 170: 985-7.
11. Sauerbruch T, Delius M, Paumgartner G, Holl J, Wess O, Weber W, Hepp W, Brendel W. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22.
12. Toom R den, Vergunst H, Nijs HGT, Brakel K, Laméris JS, Terpstra OT. Electromagnetic shock wave lithotripsy of gallbladder stones using a wide range of inclusion criteria. Am J Gastroenterol 1992; 87: 498-503.
13. Ponchon T, Barkun ANG, Pujol B, Mestas JL, Lambert R. Gallstone disappearance after extracorporeal lithotripsy and oral bile acid dissolution. Gastroenterology 1989; 97: 457-63.
14. Magnuson TH, Lillemoe KD, Pitt HA. How many Americans will be eligible for biliary lithotripsy? Arch Surg 1989; 124: 1195-1200.
15. Rege RV, Nemcek AA, Nahrwold DL. Selection of patients for gallstone lithotripsy. Am J Surg 1989; 158: 184-7.
16. Barkun ANG, Ponchon T. Extracorporeal biliary lithotripsy. Review of experimental studies and a clinical update. Ann Intern Med 1990; 112: 126-37.
17. Vergunst H, Terpstra OT, Brakel K, Laméris JS, Blankenstein M van, Schröder FH. Extracorporeal shockwave lithotripsy of gallstones. Possibilities and limitations. Ann Surg 1989; 210: 565-75.
18. Sackmann M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gallstone recurrence rate after successful shock-wave therapy. Gastroenterology 1990; 98: 392-6.
19. Villanova N, Bazzoli F, Taroni F, Frabboni R, Mazzella G, Festi D, Barbara L, Roda E. Gallstone recurrence after successful oral bile acid treatment. A 12-year follow-up study and evaluation of long-term postdissolution treatment. Gastroenterology 1989; 97: 726-31.
20. O'Donnell LDJ, Heaton KW. Recurrence and re-recurrence of gall stones after medical dissolution: a longterm follow up. Gut 1988; 29: 655-8.

21. Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Rapid dissolution of gallstones by methyl tert-butyl ether. N Engl J Med 1985; 312: 217-20.
22. Little CJ, Dale AD, Whatley JA, Wickings JA. Methyl tertiary-butyl-ether: a new chromatographic eluent. J Chromatogr 1979; 169: 381-5.
23. Scholz DG, McCullough JE, Petersen BT, Thistle JL. Gallstone recurrence following complete dissolution with oral bile acid therapy or methyl tert-butyl ether. Hepatology 1988; 8: 1372.
24. McCullough JE, Stadheim LM, Reading CC, Petersen BT, Thistle JL. Gallstone recurrence after methyl tert-butyl ether dissolution. Gastroenterology 1990; 98: A255.
25. Faulkner DJ, Kozarek RA. Gallstones: fragmentation with a tunable dye laser and dissolution with methyl tert-butyl ether in vitro. Radiology 1989; 170: 185-9.
26. Lu DSK, Ho CS, Allen LC. Gallstone dissolution in methyl tert-butyl ether after mechanical fragmentation: in vitro study. AJR 1990; 155: 67-72.
27. Lu DSK, Ho CS, Foster FS, Hunt JW, Yeung E, Ricketts J, McKinley C, Allen LC. Accelerated gallstone dissolution in methyl tert-butyl ether by sonication. An in vitro study. Invest Radiol 1992; 27: 356-61.
28. Griffith SL, Burney BT, Fry FJ, Franklin TD. Experimental gallstone dissolution with methyl tert-butyl ether and transcutaneous ultrasound energy. Invest Radiol 1990; 25: 146-52.
29. Kannegieter LS, Brandon JC, Teplick SK, Norris JA, Baker ML, Deutsch LS, Friedenberg RM. The acceleration of gallstone destruction with synchronous biliary lithotripsy and contact dissolution in vitro using three cholesterol-solubilizing solvents. Invest Radiol 1992; 27: 140-4.
30. Vergunst H, Brakel K, Nijs HGT, Laméris JS, ten Kate FJW, Schröder FH, Terpstra OT. Sequential treatment of gallbladder stones by extracorporeal shockwave lithotripsy and methyl tert-butyl ether: assessment of safety and efficacy. Submitted for publication.
31. Holl J, Sauerbruch T, Sackmann M, Pauletzki J, Paumgartner G. Combined treatment of symptomatic gallbladder stones by extracorporeal shock-wave lithotripsy (ESWL) and instillation of methyl tert-butyl ether (MTBE). Dig Dis Sci 1991; 36: 1097-101.
32. Peine CJ, Petersen BT, Williams HJ, Bender CE, Patterson DE, Segura JW, Nagorney DM, Warner MA, Thistle JL. Extracorporeal shock-wave lithotripsy and methyl tert-butyl ether for partially calcified gallstones. Gastroenterology 1989; 97: 1229-35.
33. Brakel K, Laméris JS, Nijs HGT, Terpstra OT, Steen G, Blijenberg BC. Predicting gallstone composition with CT: in vivo and in vitro analysis. Radiology 1990; 174: 337-41.
34. Kaiser C, Karatzidou K, Kruse-Jarres JD. Untersuchung der Zusammensetzung von Gallensteinen mittels Infrarotspektroskopie im Hinblick auf eine computer-tomographische Charakterisierung in vivo. Biomed Techn 1988; 33: 23-4.
35. Vergunst H, Terpstra OT, Schröder FH, Matura E. Assessment of shock wave pressure profiles in vitro: clinical implications. J Lithotripsy Stone Dis 1989; 1: 289-98.
36. Vergunst H, Terpstra OT, Schröder FH, Matura E. In vivo assessment of shockwave pressures: implications for biliary lithotripsy. Gastroenterology 1990; 99: 1467-74.
37. Vergunst H, Terpstra OT, Brakel K, Nijs HGT, Laméris JS, Kate FJW ten, Schröder FH. Biliary extracorporeal shockwave lithotripsy: short-term and long-term observations in an animal model. Submitted for publication.
38. Nealon WH, Urrutia F, Fleming D, Thompson JC. The economic burden of gallstone lithotripsy. Will cost determine its fate? Ann Surg 1991; 213: 645-50.
39. Schirmer BD, Edge SB, Dix J, Hyser MJ, Hanks JB, Jones RS. Laparoscopic cholecystectomy. Treatment of choice for symptomatic cholelithiasis. Ann Surg 1991; 213: 665-77.
40. Sackmann M, Pauletzki J, Sauerbruch T, Holl J, Schelling G, Paumgartner G. The Munich gallbladder lithotripsy study: results of the first 711 patients. Ann Intern Med 1991; 114: 290-6.

41. Ell C, Kerzel W, Heyder N, Becker V, Hermanek P, Domschke W. Piezo-electric lithotripsy of gallstones. Lancet 1987; ii: 1149-50.

42. Trotman BW, Soloway RD. Pigment vs cholesterol cholelithiasis: clinical and epidemiological aspects. Am J Dig Dis 1975; 20: 735-40.

43. van Erpecum KJ, van Berge Henegouwen, Stoelwinder B, Stolk MFJ, Eggink WF, Govaert WHA. Cholesterol and pigment gallstone disease: comparison of the reliability of three bile tests for differentation between the two stone types. Scand J Gastroenterol 1988; 23: 948-54.

44. Foerster EC, Domschke W. Gallbladder cannulation at ERCP for MTBE litholysis. Presented at the IV International symposium on biliary stone therapy. Oct 2-4 1991, Rochester, Minnesota, USA.

45. Peine CJ, May GR, Nagorney DM, Patterson DE, Segura JW, Thistle JL. Same day sequential extracorporeal shock wave lithotripsy (ESWL) and methyl tert-butyl ether (MTBE) dissolution of gallstones in dogs: effect on gallbladder mucosa and MTBE absorption. Hepatology 1986; 6: 1206.

46. McGahan JP, Tesluk H, Brock JM, Johnston R, Shaul DB. Dissolution of gallstones using methyl tertiary-butyl ether in an animal model. Invest Radiol 1988; 23: 599-603.

47. Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Cholelytholysis using methyl tertiary butyl ether. Gastroenterology 1985; 88: 122-5.

48. Adam G, Knuechel R, Vorwerk D, Held C, Guenther RW. Tissue response of the biliary and digestive system of rabbits after MTBE infusion into the gallbladder. Invest Radiol 1990; 25: 58-61.

49. van Sonnenberg E, Zakko S, Hofmann AF et al. Human gallbladder morphology after gallstone dissolution with methyl tert-butyl ether. Gastroenterology 1991; 100: 1718-23.

50. McCullough JE, Petersen BT, Soper NJ, Bender CE, LeRoy AJ, Thistle JL. Daily electromagnetic shock wave lithotripsy and methyl tert-butyl ether dissolution of gallstones in dogs. Hepatology 1988; 8: 1255.

51. Petersen BT, Bender CE, LeRoy AJ et al. Repeated piezoelectric lithotripsy and methyl tert-butyl ether dissolution of human gallstones in dogs. Hepatology 1988; 8: 1373.

CHAPTER 4

The Value of Ultrasound in the Follow-up of Patients Treated with Biliary Lithotripsy: Implications for Monitoring Patients after Nonsurgical Therapy of Gallbladder Stones

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Abstract

In order to establish the value of US in the follow-up of patients treated with extracorporeal shockwave lithotripsy (ESWL), the results of 484 US examinations from 87 patients were analyzed and related to the results of ESWL. Reliability of US to assess efficacy was investigated by comparing consecutive US examinations. Unreliable US results were found in 36 patients (41%); in 7 patients US failed to demonstrate fragments. In 9 patients (10%) unreliable US findings contributed to delayed retreatment with ESWL. To avoid errors in treatment regimen, verification of US findings is advised in case of demonstrating no fragments or fragments <5 mm. In 22 patients (25%), US findings appeared indicative for hampered stone migration. Only 2 of these 22 patients (9.1%) became free of stones compared to 32 of the remaining 65 patients (49.3%) ($p<0.01$) even though both groups had similar initial stone characteristics and similar time of follow-up. Therefore US findings such as a contracted gallbladder or a CBD >7 mm indicate poor efficacy of ESWL.

Introduction

In contrast with cholecystectomy, nonsurgical gallstone therapies affects gallstones only. Meticulous follow-up of patients treated in this way is necessary in order to assess stone fragmentation and/or clearance and possible recurrence. As a result of this follow-up, clinicians have to decide whether to cease or continue therapy or to retreat patients. For follow-up, both ultrasound (US) and oral cholecystography (OCG) can be used. US is preferred because it is harmless, cheap and highly sensitive in the detection of gallstones or its fragments. Nevertheless US has shown to be of limited value to assess precisely the number and size of gallstones (1-4). Furthermore, in case of fragmentation treatments such as extracorporeal shockwave lithotripsy (ESWL), fragments may clump together and this also may lead to less accuracy (3,5).

Follow-up is also necessary to be informed about possible complications of nonsurgical gallstone therapy. These complications are on the one hand related to the migration of stone fragments from the gallbladder to the duodenum and on the other hand to the therapy itself, for instance energy trauma in case of ESWL. US should be able to provide information concerning possible complications.

To evaluate the value of US in the follow-up of patients treated with ESWL, the following questions were addressed:

1. What is the reliability of US in the assessment of stone fragmentation and/or clearance following treatment with ESWL?
2. In which way, decisions concerning the treatment regimen are affected by unreliable US results?
3. Can US indicate hampered migration of stone fragments and therefore indicate poor efficacy of ESWL?
4. What complications caused by shockwave lithotripsy itself are detected with US?

For these purposes we analyzed retrospectively in 87 patients the post-ESWL US findings and related them to the results and complications of ESWL.

Materials and Methods

From April 1988 to July 1991, 87 patients with symptomatic gallbladder stones (27 males, 60 females, mean age 48.1 years, ± 12.1 SD; range 28-81) underwent 203 treatments with an electromagnetic lithotriptor. (Lithostar® and Lithostar plus®, Siemens AG, Erlangen, Germany) as part of an ongoing trial (6). Only patients with follow-up in our hospital were included in this study. All patients received a combination of urso- and cheno-desoxycholic acid 7-8 mg/kg bodyweight in one dose in the evening) as an adjuvant treatment.

The in- and exclusion criteria for the lithotripsy trial are listed in Table 1. Forty-five patients (52%) had a solitary stone, 27 (31%) had 2 or 3 stones and 15 (17%) had 4-10 stones prior to ESWL. The mean diameter of the largest stone was 17.4 mm ± 7.2 SD (range 5-35).

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inclusion criteria

symptomatic gallbladder stones (last biliary colic shorter than 2 years ago)
visualization of the gallbladder on oral cholecystography
up to 10 stones on ultrasonography, no upper limit for stone diameter
diameter of the largest stones > 5 mm on ultrasonography
radiolucent stones or small calcified rim (<2mm) on oral cholecystography)

exclusion criteria

acute biliary disease (cholecystitis, jaundice, cholangitis, pancreatitis, hepatitis or concomitant common bile duct stones)
elevated serum activity of liver enzymes (>2 times upper margin of reference values).
aneurysms or cysts in the shock wave path
coagulopathy
pregnancy

Table 1. Inclusion and exclusion criteria for extracorporeal shock wave lithotripsy of gallbladder stones.

US examinations were performed 7-10 days after lithotripsy. Retreatment by lithotripsy was carried out if fragments of 5 mm or larger were present. After successful treatment (fragments reduced to <5 mm) US was repeated every 3 months. When US revealed complete clearance of the stones, the adjuvant therapy with oral bile acids was continued for 3 months and subsequently stopped if the next verifying US again showed the absence of fragments in the gallbladder.

US was performed by several radiologists, not associated with the lithotripsy trial. It was performed in the fasting state on real time equipment (Aloka SSD-650, Toshiba Sonolayer SSA-270A) with 3.5 MHz or 5.0 MHz curved array or sector transducers. Sections of the gallbladder were obtained in different planes with patients in supine, left posterior oblique and erect positions. The following US findings were recorded on standardized forms:

1. The size and shape of the gallbladder, i.e. normal, contracted or hydropic. A gallbladder was considered contracted when the lumen of the gallbladder contained only calculi without normal surrounding bile. Hydrops was assumed when the transverse diameter of the gallbladder measured more than 4.5 cm (7).
2. The number and size of gallstones or fragments. Only stones with a diameter of 3 mm or larger were counted. Stones or fragments smaller than 3 mm were considered to be grit (sand). The number of stones was categorized as 1, 2, 3, 4, 5, 6-10 or more than 10 stones. Only the size of the largest stone or fragment was recorded.
3. Other US findings concerning the gallbladder and bile ducts such as: a generally thickened gallbladder wall, impaction of stones or fragments in the cystic duct or gallbladder neck; sludge, a diameter of more than 7 mm of the common bile duct, dilatation of intrahepatic bile ducts.
4. Abnormalities appearing in the liver parenchyma, the pancreas and the right kidney were also recorded.

US was considered unreliable to evaluate the number and size of gallstones when:

1. An US examination in which stones or residual fragments could not be demonstrated, was followed within 3 months by US in which stones or fragments were demonstrated, most likely not due to stone recurrence.
2. Two consecutive US examinations within 3 months, in which the last examination revealed a largest fragment diameter to be more than 3 mm larger than was measured in the former examination.
3. An examination was recorded as nondiagnostic concerning the number and size of gallstones or fragments, e.g. in case of a contracted gallbladder or aggregation of stone fragments.

The following US findings were recorded as indicative for hampered migration of stone fragments: a contracted gallbladder, hydrops of the gallbladder, diameter of common bile duct larger than 7 mm and signs of pancreatitis, such as enlargement and echopoor aspect of the pancreas or fluid collections around the pancreas.

Data analysis

Results are given as mean (range) or mean ± SD, as indicated. Continuous data were compared with the Mann-Whitney U-test. Proportions were compared using a standard test assuming two binomial distributions or with the Chi-square test.

Results

Eighty-seven patients underwent 464 post-ESWL US examinations. US examinations in 36 patients (41%) were considered unreliable concerning the assessment of stone fragmentation and/or clearance (Table 2). In 19 cases this was due to inaccurate measurements. In 7 patients US incorrectly did not demonstrate stones or fragments. In 9 patients an unreliable US examination contributed to delay in retreatment with ESWL of at least 3 months.

	number of patients	contributed to delay in retreatment with ESWL
incorrect stone free	7	-
inaccurate measurement	19	8
nondiagnostic because of:		
- contracted gallbladder	9	1
- aggregation of stone fragments	4	-
	36 (41%)*	9 (10%)

Table 2. US examinations with unreliable results concerning the stone fragmentation and/or clearance in 87 patients
* three patients had a combination of two examinations with unreliable results.

The US findings of 22 patients (25%) indicative for hampered migration of stone fragments are listed in Table 3. The most frequent findings were a contracted gallbladder in 15 patients (17%) and a common bile duct larger than 7 mm in 6 patients (7%). In 11 patients the US findings returned to normal.

Among the patients who were free of stones a statistically significant difference in the percentage ($p < 0.01$) was found between the group of 22 patients with US findings indicative for hampered stone migration (9.1%) and the remaining 65 patients without these findings (49.3%). Seven out of 22 patients (31.8%) in the group with US findings indicative for hampered stone migration underwent cholecystectomy compared to 6 out of 65 patients (9.2.%) in the group without these US findings. Cholecystectomy was performed either because ESWL was considered inadequate or because of complications of ESWL (one patient suffered from a persistent biliary pancreatitis). The two groups of patients with and without these US findings did not significantly differ in baseline stone characteristics or time of follow-up (Table 4).

US findings	patients	transient
contracted gallbladder	15	7
hydrops of the gallbladder	1	-
common bile duct >7 mm	6	4
pancreatitis	1	-
	22 *	11

Table 3. Ultrasound findings indicative for hampered migration of stone fragments
* one patient had a combination of US findings.

In two patients, the US examination one week after ESWL, showed an echo poor focal lesion of about 2 cm of the liver adjacent to the gallbladder, which was considered to be a hematoma. There were no clinical or laboratory signs of damage to the liver in these patients and the lesions disappeared spontaneously and could not be demonstrated on the next follow-up US examination.

Discussion

This study demonstrate some limitations of US to assess stone fragmentation and/or clearance in patients treated with ESWL. Limitations of US in assessing the number and size of gallstones and fragments have been ascribed to patient, technical and observer related factors (8). ESWL itself also induces additional diagnostic problems (5). In this study 13 patients (15%) had nondiagnostic US examinations concerning the assessment of efficacy because of side effects that were induced by ESWL. In 9 cases this was caused by a contracted gallbladder. In 4 patients reliable interpretation of the US examination was not possible due to clumping of fragments. Although we did not use "rollover maneuvers" to prevent clumping as advised by Khouri et al.(5), patients were examined in

	group of 22 patients with US findings indicative for hampered stone migration	group of 65 patients without US findings indicative for hampered stone migration	P value
baseline stone characteristics:			
- solitary stone	10 (45.5)*	35 (53.9)	n.s.
- 2-3 stones	8 (36.3)	19 (29.3)	
- > 3 stones	4 (18.2)	11 (16.9)	
- diameter largest stone (mm)	20.8 ± 7.8	16.2 ± 6.7	n.s.
mean time follow-up (months)	10.5 ± 6.7 (range 1-21)	12.8 ± 8.5 (range 1-36)	n.s.
therapeutic results:			
- no fragmentation	2 (9.1)	2 (3.1)	< 0.01
- < 50% decrease in diameter of the largest stone	6 (27.2)	11 (16.9)	
- > 50% decrease in diameter of the largest stone	9 (40.9)	11 (16.9)	
- grit (sand)	3 (13.6)	9 (13.8)	
- free of stones	2 (9.1)	32 (49.3)	
complications:			
- colics	9 (40.9)	22 (33.8)	n.s.
cholecystectomy	7 (31.8)	6 (9.2)	< 0.01

Table 4. Comparison of stone characteristics, results and complications in 2 groups of patients with and without US findings indicative for hampered stone migration

* percentages in parentheses

different positions including the erect position. Because the phenomenon of clumping is most evident on US within 24 hours of ESWL, we started US evaluation 7-10 days after ESWL. Therefore clumping plays a minor role in the problems associated with imaging after ESWL.

Interpretation of post-ESWL US examinations may be influenced by the so-called comet-tail artifact (9). However this artifact is only observed on US within a few days after ESWL and was not observed in this study, probably because we postponed evaluation to 7-10 days.

In evaluating the efficacy of ESWL two major questions should be addressed. Firstly to determine the necessity for retreatment with ESWL. In most protocols patients are eligible for retreatment if residual stone fragments are larger than 5 mm. Retreatment with ESWL was delayed in 9 patients (10%), because the fragment size was underestimated in 8 patients and US was nondiagnostic in 1 patient. To avoid this delay in retreatment, a verification US within a short period of time, should be performed if US reveals fragments smaller than 5 mm.

The second question concerning efficacy is the assessment of complete disappearance of stones and/or grit (sand) to cease further adjuvant therapy. In our protocol, patients free of stones continue adjuvant oral bile acid medication for three months, after which US is performed to verify the absence of stones. The necessity of this verification is proven by the outcome of this study in which the verification US examinations revealed grit or even fragments in 7 patients (8%), in spite of the former US examination in which no stones or fragments could be demonstrated. Because the verification US was performed within 3 months during oral medication of bile acids, recurrence of stone formation is unlikely (10). The reliability of US to assess stone fragmentation and/or clearance was investigated in this study by comparing consecutive US examinations. Of course, this method have limitations because a gold standard is not available. These patients normally do not undergo cholecystectomy.

This study shows that US may provide important information concerning the ultimate stone clearance after ESWL. The 22 patients with US findings indicative for hampered stone migration had significantly lesser percentages of complete stone clearance compared with the group of patients without these US findings. The most frequent US finding in these 22 patients was a contracted gallbladder in 15 patients. A contracted gallbladder as assessed with US is highly specific in predicting non-visualization of the gallbladder on oral cholecystography (11). Gallbladder visualization on OCG is required for oral treatment with bile acids because this ensures both cystic duct patency and concentration capability of the gallbladder. The utility of continuing oral medication of bile acids in patients with a contracted gallbladder is therefore very doubtful.

In this study a contracted gallbladder was found in 15 of 87 patients (17%). This is similar to the frequency of non-visualization of the gallbladder on post-ESWL OCG in 5 of 39 patients (13%) as reported by Baumgartner et al.(12), however more than Sackmann et al.(13) who reported a contracted gallbladder on US and a non-visualized gallbladder on OCG in only 5 of 175 patients (3%). Maybe this is due to the extended inclusion criteria for stone characteristics in our protocol (6).

Complications of ESWL as a result of shockwave therapy, i.e. energy trauma, are mostly mild and limited to transient microscopic hematuria and skin petechia. More serious complications that could be assessed with US are extremely rare and limited to one case report (14). Our findings of two cases with suspected liver hematoma are hard to prove, because of the absence of clinical and laboratory signs in these patients, although the temporary nature of these findings is circumstantial evidence for trauma.

We conclude that US has some limitations in assessing the efficacy of ESWL. These limitations can influence clinical management in two ways:

1. Overestimation of efficacy by incorrectly demonstrating no fragments. Therefore a verification US is advised and claims regarding success without a verification US should be regarded with caution.
2. Delay in retreatment with ESWL by underestimation of the fragment size. Therefore a verification US is advised if US reveals fragments smaller than 5 mm.

It is expected that these limitations also affects the follow-up of other nonsurgical treatment of gallbladder stones such as oral and local contact dissolution therapies.

It is furthermore concluded that US findings indicative for hampered stone migration indicate poor efficacy of ESWL. In patients with a contracted gallbladder continuing oral medication with bile acids is doubtful.

References

1. Simeone JF, Mueller PR, Ferrucci JT. Non-surgical therapy of gall stones. Implications for imaging. AJR 1989; 152: 11-7.
2. Brink JA, Simeone JF, Mueller PR, et al. Routine sonographic techniques fail to qualify gall stones size and number: A retrospective study of 111 surgically proved cases. AJR 1989; 153: 503-6.
3. Mathieson JR, Sol B, Malone DE, Becker ChD, Burhenne HJ. Accuracy of sonography for determining the number and size of gall bladder stones before and after lithotripsy. AJR 1989; 153: 977-80.
4. Garra BS, Davros WJ, Lack EE, Hozi SC, Silverman PM, Zemar RK. Visibility of gall stone fragments at US and fluoroscopy: implications for monitoring gall stone lithotripsy. Radiology 1990; 174: 343-7.
5. Khouri MR, Goldszmidt JB, Laufer I, et al. Intact stones or fragments? Potential pitfalls in the imaging of patients after biliary extracorporeal shockwave lithotripsy. Radiology 1990; 177: 147-151.
6. den Toom R, Vergunst H, Nijs HGT, Brakel K, Laméris JS, Terpstra OT. Electromagnetic shockwave lithotripsy of gallbladder stones using a wide range of inclusion criteria. Am J Gastroenterol 1992; 87: 498-503.
7. Raghavendra BN, Feiner HD, Subramanyam BR, Ranson JHC, Toden SP, Hozli SC et al. Acute cholecystitis: sonographic-pathologic analysis. AJR 1981; 137: 327-332.
8. Brakel K, Laméris JS, Nijs HGT, Ginai AZ, Terpstra OT. Accuracy of Ultrasound and Oral Cholecystography in assessing the number and size of gall stones: Implications for non-surgical therapy. Br J Radiol 1992; 54: 779-83.
9. Shapiro RS, Winsberg F. Comet-tail artifact from Cholesterol Crystals: Observations in the Postlithotripsy gall bladder and an in vitro model. Radiology 1990; 177: 153-6.
10. Sackmann M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gall stone recurrence rate after successful shockwave therapy. Gastroenterology 1990; 98: 392-6.
11. Brakel K, Laméris JS, Nijs HGT, Ginai AZ, Terpstra OT. The value of ultrasound in predicting non-visualization of the gallbladder on OCG: Implications for imaging strategies in patient selection for non-surgical therapy of gall stones. Clin Radiol 1991; 43: 186-9.
12. Baumgartner BR, Jones MT, Torres WE, Nelson RC, Peterson JE.
Comparison of Ultrasonography and Oral Cholecystography in Lithotripsy.
II Determining Retreatment. Invest Rad 1991; 26: 636-9.
13. Sackmann M, Delius M, Sauerbruch T et al. Shock-wave lithotripsy of gall bladder stones, The first 175 patients. N Engl J Med 1988; 318: 393-7.
14. McGrath FP, Lee SH, Gibney RG, Burhenne HJ. Hepatic subcapsular hematoma: an unusual complication of biliary lithotripsy. AJR 1990; 154: 1015-6.

CHAPTER 5

Which Treatment for the Patient with Symptomatic Gallbladder Stones?

An Analysis of Treatment Options

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Abstract

Gallbladder stones represent a major clinical health problem in western society. Until recently, cholecystectomy was the only therapeutic option for patients with symptomatic gallbladder stones. In the last decade several alternative treatments have been developed. The aim of this study was to evaluate the percentage of patients suitable for these treatments. We analyzed 694 patients visiting the gallstone outpatient clinic of the Dept of Surgery of the University Hospital Rotterdam-Dijkzigt (April 1988 - October 1991) and established the eligibility percentages of these patients for the seven most commonly used treatments for symptomatic cholelithiasis. These eligibility percentages were: 97.1% for the 'classical' cholecystectomy, 86.2% for laparoscopic cholecystectomy, 27.7% for dissolution by orally administered bile acids, 37.0% for local contact dissolution by methyl *tert*-butyl ether, 18.1% for extracorporeal shock wave lithotripsy and adjuvant treatment with oral bile acids, 40.1% for percutaneous cholecystolithotomy, and 43.5% for rotary contact lithotripsy.

Regarding the inclusion percentages, success percentages, complication rates and risk of stone recurrence laparoscopic cholecystectomy is probably the best treatment for patients with symptomatic gallbladder stones without an increased risk for surgery. However, a place will remain for non-operative treatment in patients with a high operative risk or for patients who insist on non-invasive treatment.

Introduction

Gallbladder stone disease represents a major clinical health problem in western society. Epidemiological studies demonstrate a prevalence of about 10% (1-3). Most of the gallbladder stones remain asymptomatic and do not need any treatment (4-6). Cholecystectomy was first performed on July 15, 1882 by Carl Langenbuch in Berlin (7). For symptomatic gallbladder stones this operation is still the gold standard. Nowadays cholecystectomy has a morbidity rate of 10-30% and a mortality rate of 0.1-0.3% which increases to 5% or more for patients older than 70 years (8). A variety of alternative treatments has been developed during the last two decades to diminish morbidity and mortality especially in high-risk patients: laparoscopic cholecystectomy (9), dissolution of gallbladder stones with orally administered bile acids (10), local contact dissolution with methyl *tert*-butyl ether (MTBE) (11), extracorporeal shock wave lithotripsy (ESWL) and adjuvant treatment with oral bile acid therapy (12), percutaneous cholecystolithotomy (PCCL) (13), and rotary contact lithotripsy (14). As so many treatment options are available it is important to know what percentage of patients is eligible for each of these different treatment modalities.

The aim of this study was to establish eligibility percentages for each therapeutic modality based on the results of an analysis of 694 patients visiting the gallstone outpatient clinic of the University Hospital Rotterdam-Dijkzigt.

Patients and Methods

The medical files of 694 consecutive patients who visited the gallstone outpatient clinic from April 1988 to October 1991 were reviewed. In taking the patient's history special attention was paid to symptomatology, concomitant disease, previous operations and the patient's preference for therapy. Gallbladder stones were considered to be symptomatic when the patients fulfilled the criteria of the Roma Working group: pain lasting longer than 15 minutes and shorter than 12 hours, usually located in the epigastrium and/or right upper quadrant, sometimes radiating to the back, in the absence of other abnormalities which could explain these abdominal complaints (15). Each patient underwent a physical examination. Analysis was extended by laboratory tests and radiological examination if the patients were symptomatic. Laboratory tests consisted of white blood cell count, serum levels of hemoglobin, total bilirubin, cholesterol, alkaline phosphatase, aspartate and alanine aminotransferase, gamma-glutamyltranspeptidase, and amylase. Also radiological examinations were subject to a protocol, i.e. both ultrasound (US) and oral cholecystography (OCG) and in some patients computerized tomography (CT) of the gallbladder. The latter two were carried out only if the patient preferred an alternative non-surgical treatment. On ultrasonography the appearance of the gallbladder (normal, collapsed, hydrops), the number of gallstones and the diameter of the largest stone were assessed. When there was gallbladder wall thickening, grit (concrements <3 mm), sludge, stone impaction or a dilated common bile duct (>7 mm), this was also recorded. On oral cholecystography the patient's preparation (contrast in the gallbladder and/or in the small bowel), opacification of the gallbladder, the number of gallstones, the diameter of the largest stone, the presence of calcifications (whole stone; core; rim >2mm; rim <2mm) and the presence of floating stones were assessed routinely. CT-scanning of the gallbladder was performed in the first 50 patients who had an OCG to compare these radiologic methods in predicting the amount of cholesterol and calcium in the gallbladder stones (16).

OCG was not carried out if the patient refused ESWL as a therapeutic option, or if results of previous US examination excluded the patient from ESWL and adjuvant oral bile acid therapy. Based upon these data, eligibility for the seven different therapeutic modalities for gallstone disease was established. The inclusion and exclusion criteria for the different treatment modalities we used were collected from the literature. The exclusion criteria for 'classical' open cholecystectomy were: increased operative risk (ASA III or IV) (17,18). Absolute contraindications for laparoscopic cholecystectomy were: increased operative risk (ASA III or IV), collapsed and fibrotic gallbladder, previous upper abdominal surgery or pregnancy. Relative contraindications were: acute biliary disease, concomitant common duct stones, portal hypertension, major clotting disorders or morbid obesity (17,19). Contraindications for bile acid therapy were: a collapsed gallbladder, calcifications of the stones, acute biliary disease (p.e. acute hepatitis, cholecystitis, cholangitis, pancreatitis, obstruction of the common bile duct), biliary colics within 1 month before starting treatment, non-visualization of the gallbladder on OCG, diameter largest stone >15 mm, elevated serum activity of liver enzymes or pregnancy (20,21). Contraindications for direct contact dissolution with MTBE were: acute biliary disease, a collapsed gallbladder, rim calcifications of the stones larger than 2mm, non-visualization of the gallbladder on OCG, coagulopathy, pregnancy or chronic active liver disease (22,23). Contraindications for extracorporeal shock wave lithotripsy were: more than 3 stones, diameter of the largest stone greater than 30 mm or less than 5 mm, calcified stones, a collapsed gallbladder, acute biliary disease, coagulopathy, pregnancy (24). Contraindications for percutaneous cholecystolithotomy were increased operative risk (ASA III or IV), collapsed gallbladder, previously performed upper abdominal surgery or non-visualization on OCG (25). Contraindications for percutaneous rotary lithotripsy were: collapsed gallbladder, non-visualization on OCG, gallstone impaction or diameter of largest stone >25mm (14).

Results

Between April 1988 and October 1991 .694 patients visited the gallstone outpatient clinic. One hundred and thirty-five of these patients were not included in the study for the following reasons: 94 patients were asymptomatic, 18 patients refused further analysis after their first visit, in 9 patients the stones had passed through the cystic duct whereafter the symptoms had disappeared, 9 patients had gallbladder polyps instead of stones, 4 patients had a pathologic gallbladder or adenomyomatosis on ultrasound, and one patient had a history of previous cholecystectomy. Thus 559 patients were suitable for analysis of eligibility for the seven different therapies of gallbladder stones. The mean age was 48 yr (range: 20-88), male:female ratio was 1:3.5, the mean height was 167 cm (range 143-194), and the mean weight was 73 kg (range: 45-165). One hundred and sixty-four patients had 1 stone (29%), 62 patients had 2 stones (11%), 36 patients had 3 stones (7%) and 297 patients had 4 or more stones (53%). The mean diameter of the largest stone was 15 mm (range 3-45). Calcifications of the stones were detected in 99 of 389 (25%) OCG's, 37 stones had a generalized calcification, 16 stones had a calcified nucleus, 20 stones had a rim calcification larger than 2 mm and 26 stones had a rim calcification smaller than 2 mm. After matching the characteristics of the patients with the aforementioned inclusion and exclusion criteria we calculated the eligibility percentages.

From 559 patients 534 (97.1%) were eligible for cholecystectomy by laparotomy, 482 (86.2%) for laparoscopic cholecystectomy, 155 (27.7%) for dissolution by oral bile acids, 207 (37.0%) for local contact dissolution by methyl *tert*-butyl ether (MTBE), 101 (18.1%) for extracorporeal shock wave lithotripsy (ESWL) and adjuvant treatment with oral bile acids, 224 (40.1%) for percutaneous cholecystolithotomy (PCCL), and 243 (43.5%) for rotary contact lithotripsy (Fig. 1).

Discussion

The treatment of gallbladder stones has changed dramatically in the last decade. First there is more or less consensus of treating patients with symptomatic gallbladder stones only. Second the standard treatment of gallbladder stones, i.e. cholecystectomy by laparotomy was the only therapeutic option for symptomatic cholelithiasis for almost a century. Although the morbidity and mortality of cholecystectomy are low, many alternative treatment modalities have been developed especially for the high-risk patients or those patients who do not want to undergo a laparotomy (9-14). The challenge for alternative treatments is to minimize the discomfort for the patient without diminishing the good results of cholecystectomy. We have chosen those treatment modalities which are therapeutic options for symptomatic gallbladder stones: 'open' cholecystectomy, laparoscopic

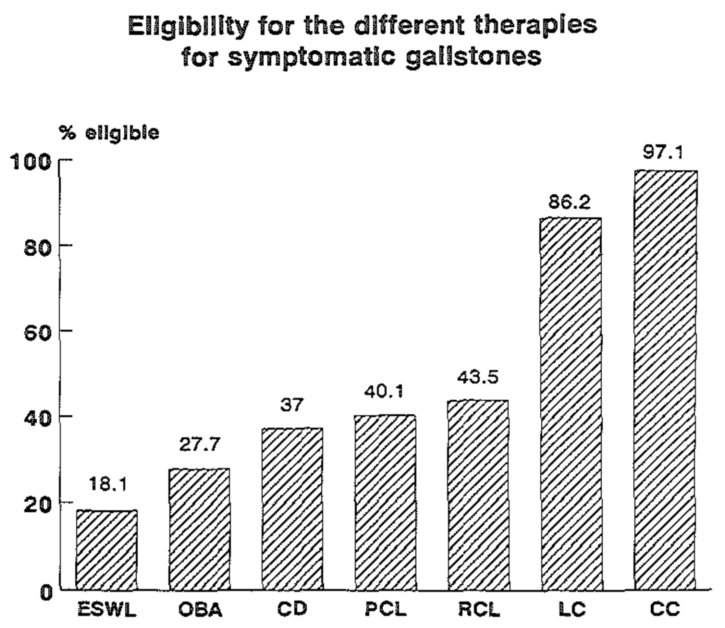

Figure 1. Eligibility percentages for the treatment options for symptomatic gallbladder stones assessed after analysis of 694 patients visiting the gallstone outpatient clinic of the Dept of Surgery of the University Hospital 'Dijkzigt' Rotterdam, The Netherlands.

ESWL = extracorporeal shock wave lithotripsy; OBA = oral bile acids; CD = local contact dissolution with methyl tert-butyl ether; PCL = percutaneous cholecystolithotomy; RCL = rotary contact lithotripsy; LC = laparoscopic cholecystectomy; CC = 'classical' cholecystectomy.

cholecystectomy, dissolutiontherapy with oral bile acids, local contact dissolution with methyl *tert*-butyl ether (MTBE), extracorporeal shock wave lithotripsy (ESWL) with adjuvant treatment with oral bile acids, percutaneous cholecystolithotomy (PCCL), and rotary contact lithotripsy. Each of these therapies has its specific in and exclusion criteria. Because it is important to know how many patients will be suitable for these treatments, we made an analysis of 694 patients visiting the gallstone outpatient clinic of the University Hospital Rotterdam-Dijkzigt to establish the eligibility percentages for each therapeutic modality.

We found that 97.1% of the patients would be suitable for 'classic' cholecystectomy, 86.2% for laparoscopic cholecystectomy, 43.5% for rotary contact lithotripsy, 40.1% for percutaneous cholecystolithotomy, 37% for MTBE, 27.7% for oral bile acids, and 18.1% for ESWL. We will now discuss the advantages and disadvantages of these treatments in brief.

General anesthesia is necessary in 'open' cholecystectomy and laparoscopic cholecystectomy. Also in some cases of ESWL and PCCL general anesthesia is used. With the second and third generation lithotriptors which are mostly used nowadays, general anesthesia is not necessary and treatments are carried out under intravenous analgesia and/or sedation or even without any analgesia (24,26-27). PCCL can be very painful and in complicated cases can last for several hours, then there can be an indication for general anesthesia. Local contact dissolution with MTBE and rotary contact lithotripsy are performed under local anesthesia combined with intravenous analgesia and eventually sedation. Evidently dissolution therapy with oral bile acids requires no analgesia.

Cholecystectomy and laparoscopic cholecystectomy have a 100% success rate in the removal of gallbladder stones and there is no chance of recurrence of gallbladder stones. PCCL and rotary contact lithotripsy are successful in removing gallbladder stones in 90% and 50% of the cases respectively (14,25). Nineteen-fifty percent of the patients had a stonefree gallbladder after 2 years of dissolution therapy with urso and/or chenodeoxycholic acid (20,21). Local contact dissolution with MTBE resulted in a completely stonefree gallbladder in 41-84% of the patients and 96% of the patients had a stonefree gallbladder or more than 95% dissolution after 6 months follow-up (22,23). Recently Sackmann et al. presented the Munich experience with 711 patients treated by ESWL and adjuvant oral bile acid therapy. The rate of complete fragment clearance 9-12 months after ESWL were: 60-83% for solitary stones (diameter < 20 mm); 32-63% for solitary stones (diameter 21-30 mm) and 16-46% for 2-3 stones (maximum total diameter 30 mm). The variations in the results were due to different types of lithotriptors and different energy levels of the lithotriptor in the groups (24). Although the results of the latter three therapies are less, one has to consider that ESWL with adjuvant oral bile acid therapy and especially dissolution with oral bile acids are the most patient-friendly therapies causing the least discomfort. Besides this fact, these therapies can be carried out as outpatient treatments.

The problem with all gallbladder stone therapies leaving the gallbladder *in situ* is the risk of recurrence of the gallbladder stones. Recurrence of stones is more likely in cases with initially multiple stones in the gallbladder. In most of the alternative treatments the follow-up is still too short, but the first recurrence notes after dissolution with oral bile acids are 13% after 1 year increasing up to 50-60% after 10 years (28-30). After ESWL and adjuvant treatment with oral bile acids these numbers are 15% after 2 years (31) and after local contact dissolution with MTBE the preliminary recurrence rates are 15% after 9 months up to 40% after 2 years (32,33).

'Classical' cholecystectomy has a morbidity rate of 10-30% and a mortality rate of 0.1-0.3%, the latter rising to 5% or more in patients over 70 years of age (8). Only one large series of laparoscopic cholecystectomy has been published yet which presents a complication rate of 5.1%, a conversion percentage to conventional cholecystectomy of 4.7% and a mortality rate of 0.07% (19). Bile acids, especially chenodeoxycholic acid can be hepatotoxic. Transient elevation of serum aminotransferases was reported in 30% of the patients (34). Especially with chenodeoxycholic acid about 25% of the patients suffers from diarrhoea which decreases after reducing the dosage. More research is needed to evaluate the possible atherogenic effects of oral bile acids. No mortality has been reported during treatment with orally administered bile acids (20,21). Local contact dissolution with MTBE has a morbidity rate of 30-35%, whereas no mortality has been described so far (22,23). ESWL followed by oral bile acids has a morbidity rate of about 35% (24). So far mortality after ESWL was not been published in the literature but in the Third International Symposium on Biliary Lithotripsy in Munich (1990), 4 cases of mortality after ESWL were reported. Three patients died of pancreatitis and 1 patient died of myocardial infarction, one day after ESWL. Results of percutaneous cholecystolithotomy are scarce. Chiverton reported a conversion rate to cholecystectomy of 7% and a complication rate of 12% without mortality (25). Large series of rotary contact lithotripsy are not yet available. Miller et al. reported the treatment results of the first ten patients. One major complication occurred (phlegmonous cholecystitis) resulting in a cholecystectomy and 4 minor complications were encountered, mostly due to cholecystostomy catheter dislodgement. There was no mortality in this small study (14).

The ideal therapy for symptomatic gallbladder is painless, should be performed without general anesthesia, has a 100% success rate, no morbidity, no mortality, no complications, no recurrence of stone formation, and low costs. Although such a therapy will remain an utopia, much research has been carried out to create a number of treatment modalities. The physician's dilemma is to choose between the approaches that are the most suitable for that particular patient and the patient's preference. The latter is a point which is underestimated and seldom mentioned in the literature, but the patient's preference is an important cause of non-operative therapy.

The introduction of laparoscopic cholecystectomy has decreased the territory of non-operative techniques. Laparoscopic cholecystectomy combines a high inclusion percentage with a high success rate, no risk of stone recurrence and a low complication rate. The inclusion percentage is thought to increase and the complication rate to decrease with growing experience. Because of the short hospital stay or even day-case outpatient-treatment, no retreatments and no risk of stone recurrence, laparoscopic cholecystectomy is probably in the long term the most economic therapy. The role of 'classical' cholecystectomy will decrease after the successful introduction of laparoscopic cholecystectomy. However, it will always remain necessary to gain experience with cholecystectomy by laparotomy in the case of conversion of laparoscopic cholecystectomy or when inflammation, adhesions, carcinoma or anatomical variants make laparoscopic cholecystectomy impossible.

In summary it is our opinion that laparoscopic cholecystectomy is the best therapeutic option for patients with symptomatic gallbladder stones. A place will remain, albeit small, for non-operative treatment in the future, especially for patients with a high operation risk or when there is a patient's preference for non-surgical therapy. However, of this specific group of patients only a small number will be suitable for non-surgical treatment, due to the narrow inclusion criteria. Owing to the low inclusion percentage and low success rate with long treatment time combined with high costs, we agree with Cushieri that the only indication for oral bile acids is as adjuvant treatment after ESWL or MTBE (35). ESWL and MTBE seem to be good alternatives for high risk patients or when patients refuse surgery as therapy. It may be that the inclusion percentages and the efficacy can be enhanced by combining these two therapies sequentially or simultaneously (36,37). We think that PCCL, under general anesthesia is no longer a viable alternative after the introduction of laparoscopic cholecystectomy. The experience with rotary contact lithotripsy is still limited and the proper place of this technique has yet to be established. It seems an effective and safe therapy especially for high-risk operation patients not suitable for ESWL and MTBE. Due to a decrease in the demand for non-operative techniques and due to the low inclusion percentages of these therapies we think it is necessary to concentrate the expertise with these techniques in a few specialist centers.

Finally, it is our opinion that laparoscopic cholecystectomy will become or already is the new gold standard in the treatment of symptomatic gallbladder stones.

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References

1. Barbara L, Sama C, Morselli Labate AM. A population study on the prevalence of gallstone disease: the Sirmione study. Hepatology 1987; 7: 913-7.
2. Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). Prevalence of gallstone disease in an Italian adult female population. Am J Epidemiol 1984; 119: 796-805.
3. Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). The epidemiology of gallstone disease in Rome, Italy. Part II. Factors associated with the disease. Hepatology 1988; 8: 907-13.
4. Finlayson N. Cholecystectomy for gallstones. A good thing if they cause symptoms. Br Med J 1989; 298: 133-4.
5. Ransohoff DF, Gracie WA, Wolfenson LW. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 1983; 99: 199-204.
6. Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). Radiologic appearance of gallstones and its relationship with biliary symptoms and awareness of having gallstones. Observations during epidemiological studies. Dig Dis Sci 1987; 32: 349-53.
7. Langenbuch C. Ein Fall von Extirpation der Gallenblase wegen chronischer Cholelithiasis. Heilung. Berliner Klin Wochenschr 1882; 19: 725-7.
8. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989; 158: 174-8.
9. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. Preliminary report of 36 cases. Ann Surg 1990; 211: 60-2.
10. Danzinger RG, Hofmann AF, Schoenfield LJ, Thistle JL. Dissolution of cholesterol gallstones by chenodeoxycholic acid. N Engl J Med 1972; 286: 1-8.
11. Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Rapid dissolution of gallstones by methyl tert-butyl ether. N Engl J Med 1985; 312: 217-20.
12. Sauerbruch T, Delius M, Paumgartner G, Holl J, Wess O, Weber W, Hepp W, Brendel W. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22.
13. Kellett MJ, Wickham JEA, Russell RCG. Percutaneous cholecystolithotomy. Br Med J 1988; 296: 453-5.
14. Miller FJ, Rose CS, Buchi KN, Hunter JG, Nash JE, Kensey KR. Percutaneous rotational contact biliary lithotripsy: initial clinical results with the Kensey Nash Lithotrite. Radiology 1991; 178: 781-5.
15. Schoenfield LJ, Carulli N, Dowling RH et al. Roma 88 working team report. Gastroenterology Int 1988; 1: 17-24.
16. Brakel K, Laméris JS, Nijs HGT, Terpstra OT, Steen G, Blijenberg BC. Predicting gallstone composition with CT: in vivo and in vitro analysis. Radiology 1990; 174: 337-41.
17. Gadasz TR, Talamini MA. Traditional versus laparoscopic cholecystectomy. Am J Surg 1991; 161: 336-8.
18. Keats AS. The ASA classification of physical status - a recapitulation. Anesthesiology 1978; 49: 233-6.
19. The Southerns Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991; 324: 1073-8.
20. Schoenfield LJ, Lachin JM, the Steering Committee and the National Cooperative Gallstone Study Group. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone Study. A controlled trial of efficacy and safety. Ann Int Med 1981; 95: 257-82.
21. Podda M, Zuin M, Battezzati PM, Ghezzi C, de Fazio C, Dioguardi ML. Efficacy and safety of a combination of chenodeoxycholic acid and ursodeoxycholic acid for gallstone dissolution: a comparison with ursodeoxycholic acid alone. Gastroenterology 1989; 96: 222-9.
22. Thistle JL, May GR, Bender CE et al. Dissolution of cholesterol gallbladder stones by methyl tert-butyl ether administered by percutaneous transhepatic catheter. N Engl J Med 1989; 320: 633-9.
23. Leuschner U, Hellstern A, Schmidt K et al. Gallstone dissolution with methyl tert-butyl ether in 120 patients - efficacy and safety. Dig Dis Sci 1991; 36: 193-9.

24. Sackmann M, Pauletzki J, Sauerbruch T, Holl J, Schelling G, Paumgartner G. The Munich gallbladder lithotripsy study: results of the first 711 patients. Ann Intern Med 1991; 114: 290-6.

25. Chiverton Sg, Inglis JA, Hudd C, Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy: the first 60 patients. Br Med J 1990; 300: 1310-2.

26. Toom R den, Vergunst H, Nijs HGT, Brakel K, Laméris JS, Terpstra OT. Electromagnetic shock wave lithotripsy of gallbladder stones using a wide range of inclusion criteria. Am J Gastroenterol 1992; 87: 498-503.

27. Ell C, Kerzel W, Heyder N, Becker V, Hermanek P, Domschke W. Piezo-electric lithotripsy of gallstones. Lancet 1987; ii: 1149-50.

28. Villanova N, Bazzoli F, Taroni F, Frabboni R, Mazzella G, Festi D, Barbara L, Roda E. Gallstone recurrence after successful oral bile acid treatment. A 12-year follow-up study and evaluation of long-term postdissolution treatment. Gastroenterology 1989; 97: 726-31.

29. O'Donnell LDJ, Heaton KW. Recurrence and re-recurrence of gall stones after medical dissolution: a longterm follow up. Gut 1988; 29: 655-8.

30. Ruppin DC, Dowling RH. Is recurrence inevitable after gallstone dissolution by bile-acid treatment? Lancet 1982; i: 181-5.

31. Sackmann M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gallstone recurrence rate after successful shock-wave therapy. Gastroenterology 1990; 98: 392-6.

32. Scholz DG, McCullough JE, Petersen BT, Thistle JL. Gallstone recurrence following complete dissolution with oral bile acid therapy or methyl tert-butyl ether. Hepatology 1988; 8: 1372.

33. McCullough JE, Stadheim LM, Reading CC, Petersen BT, Thistle JL. Gallstone recurrence after methyl tert-butyl ether dissolution. Gastroenterology 1990; 98: A255.

34. Lanzini A, Northfield TC. Review article: bile acid therapy. Aliment Pharmacol Therap 1990; 4: 1-24.

35. Cushieri A. Non surgical options for the management of gallstone disease. Surg Endosc 1990; 4: 127-31.

36. Peine CJ, Petersen BT, Williams HJ et al. Extracorporeal shock-wave lithotripsy and methyl tert-butyl ether for partially calcified gallstones. Gastroenterology 1989; 97: 1229-35.

37. Holl J, Sauerbruch T, Sackmann M, Pauletzki J, Paumgartner G. Combined treatment of symptomatic gallbladder stones by extracorporeal shock-wave lithotripsy (ESWL) and instillation of methyl tert-butyl ether (MTBE). Dig Dis Sci 1991; 36: 1097-101.

CHAPTER 6

Prevalence and Prevention of Gallbladder Stone Recurrence after Gallbladder Saving Therapies

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6.1 Prevalence of gallbladder stone recurrence

Cholecystectomy, introduced in 1882, was the only treatment for gallbladder stone disease for about a century (1). Cholecystectomy is a very effective and safe therapy with a morbidity of 5-30% and a mortality of 0.1-0.3% (2). Despite these good results several alternative non-surgical treatment modalities have been developed the last two decades. Dissolution of gallstones by orally administered bile acids (urso and chenodeoxycholic acid) was introduced in the 1970's (3). Although this therapy was non-invasive and safe, the inclusion rate for patients was low (15-25%) and the results in larger series were disappointing (20-50% total stone clearance after 2 years of dissolution therapy) (4,5). Hereafter several non-invasive and invasive treatments were developed. Extracorporeal shock wave lithotripsy (ESWL), local contact dissolution with methyl *tert*-butyl ether (MTBE), percutaneous cholecystolithotomy (PCCL), and rotary contact lithotripsy are all non-surgical gallbladder saving therapies (6-9).

With all gallbladder saving therapies there is a risk of recurrence of stones after successful treatment. Why some patients develop recurrent gallbladder stones and others do not is still an unsolved problem. Reports in the literature disagree about risk factors, or were not able to detect any determinant such as age, gender, race, diet, weight etc, etc (10-15).

After dissolution of stones by oral bile acids Villanova et al. found a recurrence rate of 12.5% after 1 year increasing to 61% after 11 years (11). Other authors confirmed their results. O'Donnell et al. reported a 13% recurrence after 1 year increasing up to 49% after 11 years (13). and Ruppin et al. found 50% recurrence after 7.5 years (12). These high percentages can be overestimated because dissolution results and the decision to stop dissolution therapy were only evaluated by oral cholecystography instead of ultrasonography. Thus it could be that there remained small fragments or grit in the gallbladder after total stone clearance was detected on oral cholecystography. It is now recognized that ultrasonography is superior to oral cholecystography in the detection of gallbladder stones (16-20). Therefore many dissolution therapies may have been stopped too early and did not give reliable recurrence rates.

Recurrence rates after the aforementioned non-operative therapies are still preliminary because most of these treatments were only introduced recently. Follow-up after ESWL with adjuvant oral bile acids is still short. The largest follow-up series is from the Munich group. They found a recurrence rate of 15% after 2 years (21). The follow-up after contact dissolution with MTBE and adjuvant treatment with oral bile acids is also short. The Mayo group reported recurrence rates of 15% after 9 months raising to 40% after 2 years (22,23). Freeny published a recurrence rate of 63% after successful contact dissolution with MTBE (24). Chiverton et al. reported 2 cases of recurrence after successful

PCCL in 56 patients (25). Cholecystolithotomy by laparotomy has been abandoned from the treatment tableau for gallbladder stone disease mainly because of high recurrence rates. Norrby et al. reported 50% recurrence of stones after 3 years increasing to 83% after 15 years (26).

Three to four times higher recurrence percentages after gallbladder saving therapies were found when initially multiple stones were treated (11,27,28). The reason for this phenomenon is not apparent. It has been suggested that there could be a greater number of nucleation defects or more seeding agents, or both, thus increasing the probability of re-forming gallstones (11).

Not all recurrent gallbladder stones are symptomatic. The number of patients in recurrence studies is small. Preliminary results showed that percentages of symptoms due to recurrence of gallbladder stones vary from 0-100%. Because not all recurrent stones give symptoms, long-term ultrasonographic follow-up is recommended after successful dissolution therapy (10,12,18,19,21).

6.2 Prevention of gallbladder stone recurrence

Non-invasive

History has clearly shown that simple stone removal with preservation of the gallbladder will result in significant stone recurrence. Thus recurrence of stones after gallbladder saving therapies seems to be inevitable. "Seems", because a great deal of research has been done in preventing the recurrence of stones after successful dissolution or removal of gallbladder stones. Medical, chemical, and invasive techniques are topics of study. Of course simple potential risk factors for gallstone formation such as estrogen use, dietary cholesterol, clofibrate, and rapid weight loss have to be eliminated in the first place.

Thistle et el. have shown that bile returned rapidly to a supersaturated state after discontinuance of oral bile acid therapy (29). Therefore continuation with lower dose bile acids after complete stone dissolution has been tried to prevent new stone formation. Marks et al. could not detect any effect on stone recurrence of chenodiol (375 mg/day) vs placebo in the randomized, double blind National Cooperative Gallstone Study (30). Some positive effects of chenodeoxycholic or ursodeoxycholic acid were reported in smaller non-randomized studies (11,31).

Hood et al. reported the lower prevalence of gallstone recurrence in patients regularly using aspirin (or other NSAID drugs) in a retrospective study (14). Prospective randomized studies have to be carried out to confirm the promising recurrence limiting capacities of NSAID drugs. Beta-hydroxy-beta-methylglutaryl coenzyme A reductase (HMG-CoA reductase) is the rate-limiting enzyme in the biosynthesis of cholesterol. HMG-CoA reductase inhibitors, such as lovastatin, pravastatin, and simvastatin were developed as hypocholesterolemic agents especially for use in cardiovascular disease. It is known that hypocholesterolemic agents (e.g. clofibrate) increase the output of cholesterol into bile and therefore predispose to gallstone formation (32-34). Studies have been published on the effects of HMG-CoA reductase inhibitors on biliary lipid secretion and bile acid metabolism (35-37). To our knowledge there are no clinical studies on the effect of HMG-CoA reductase inhibitors on gallstone recurrence after successful dissolution therapy. One of the major reasons is probably the high costs associated with HMG-CoA reductase inhibitors therapy.

Invasive

Gallstone recurrence can be expected after gallbladder saving therapies due to a functioning gallbladder with a patent cystic duct (12). Invasive techniques for prevention of gallbladder stone recurrence are (chemical) ablation of the gallbladder mucosa and/or occlusion of the cystic duct. Most of the investigations published on this subject are studies in laboratory animals.

Destruction of the gallbladder mucosa and fibrosis was reported after instillation of several solutions: diatrizoate meglumine (100^{0}C), ethyl alcohol, morrhuate sodium and tetracyclin and mixtures of these different agents (38-40). Application of chemical agents to the gallbladder mucosa implies the risk of systemic absorption and toxic effects. Remley et al. studied the systemic absorption of two sclerosing agents, 95% ethanol and tetracycline applied to the rabbit gallbladder. They found that absorbed systemic doses of either ethanol or tetracycline exposed to the gallbladder mucosa for as long as 30 minutes are within acceptable limits as established for human toxicity (39). Becker et al. found no detectable serum levels of ethanol after 20 minutes exposure of the porcine gallbladder to 70% ethanol. With 95% ethanol, moderate systemic ethanol absorption was detected in three of ten pigs, but these serum levels were within acceptable limits as established for toxicity in humans (41). Brakel et al. studied gallbladder ablation in 20 pigs with 96% ethanol with 3% sodium tetradecyl sulfate. Serum ethanol concentration did not reach the detection rate (0.1 gr/L) in any animal (42). Thus it seems that sclerosing agents (ethanol and tetracycline) are absorbed systemically but that the serum concentrations remain under the toxicity levels.

The goal for cystic duct occlusion is threefold: 1) to prevent flow of toxic substances into the duodenum during gallbladder mucosa ablation; 2) to prevent flow of bile into the gallbladder lumen which will likely interfere with obliteration of the lumen; 3) to prevent reepithelialization following successful gallbladder mucosa obliteration which is probably due to ingrowth of epithelium from the intact mucosa of the cystic duct (43-44).

The first feasibility studies of gallbladder obliteration and cystic duct occlusion were done in rabbits. Salomonowitz et al. succeeded in cystic duct occlusion by injecting 0.3 mL of cyanoacrylate-nitrocellulose 2% wt/wt and gallbladder ablation with diatrizoate (100^{0}C) and absolute alcohol. Criticism of this study is that the follow-up was only 2 weeks and therefore no information was obtained considering reepithelialization (38). Getrajdman et al. occluded the cystic duct by a metal hemoclip and later by a silk ligature whereafter gallbladder ablation was achieved with 95% ethanol with either 2M% or 5M% trifluoroacetic acid. In the hemoclip study reepithelialization was found originating from the intact cystic duct whereas in the silk ligature study this phenomenon was not observed (40-44).

Brakel et al. developed a triple lumen catheter which was suitable for a temporary cystic duct occlusion. However the single step treatment with 96% ethanol with 3% sodium tetradecyl sulfate and temporary cystic duct occlusion in 20 pigs did not result in complete mucosal destruction and therefore gallbladder ablation was not achieved. In contrast to Getrajdman et al., they did not observe mucosal regeneration from the cystic duct. They found multiple islands of undestroyed mucosa which acted as regeneration "nests" (42). Leahy et al. described a successful method for chemical cholecystectomy in pigs. Obliteration of the cystic duct by bipolar electrocoagulation and delayed instillation of tetracyclin in the gallbladder at 14 days produced complete destruction of all gallbladder epithelium. This study demonstrated that complete cystic duct occlusion was observed after 10 days. This was probably the reason why tetracyclin instillation immediately after cystic duct coagulation was only partially effective. Electrocoagulation and saline instillation were associated with mucocele formation (45).

Saini reported cystic duct obliteration with the use of a holmium-yttrium-aluminum-garnet laser. Although this technique was also effective, the thermal damage extended to the cystic artery and veins in 10 out of 11 pigs (46). Becker and colleagues developed a catheter with which it was possible to achieve a long-term occlusion of the porcine duct by using endoluminal radio-frequency electrocoagulation of the cystic duct. There was no epithelial regeneration or recanalization of the fibrotic cystic duct. There was no damage to the cystic artery and veins due to electrocoagulation (47). After insertion of this catheter and coagulating the cystic duct Becker et al. treated 20 pigs with ethanol and sodium tetradecyl-sulfate which resulted in gallbladder ablation without toxic side effects in almost all pigs. Encouraged by this outcome they began a clinical study in 9 selected high-risk patients treated with cholecystostomy for acute gallbladder disease. Their interesting work is reported here in more detail. After removal of the stones and after the acute inflammation had settled, cystic duct occlusion was carried out by electrocoagulation without analgetic medication on an outpatient basis. Three patients needed repeat electrocoagulation. Total occlusion of the cystic duct was achieved in all patients. Hereafter sclerotherapy of the gallbladder was performed using

95% ethanol and 3% sodium tetradecyl sulfate in 1-4 sessions per patient. This was also an outpatient treatment without pain medication. Cholecystostomy drains were removed when the production was less than 20 mL/day. Follow-up was achieved at 6-23 months. One patient died of a cerebrovascular accident. Seven patients have no complaints, one has intermittent atypical right upper quadrant pain. Ultrasonography studies showed no stone recurrence in any of the patients but the lumina of the gallbladders remained visible in all patients (median volume: 4mL). Histological biopsies taken through the cholecystostomy showed epithelial regeneration. The most likely explanation for this discrepancy between the animal and the clinical study lies in the histological differences between the nondiseased gallbladder of a young animal and a severely inflamed human gallbladder. Becker et al. concluded that electrocoagulation of the cystic duct is a safe and effective technique and obliteration of the gallbladder with ethanol and sodium tetradecyl sulfate can be performed on an outpatient basis, without pain medication, and without local or systemic toxic effects. However complete ablation of the gallbladder can not be achieved in this way. Further technical improvement will be necessary to achieve more effective obliteration of the gallbladder lumen in a shorter period and in all cases before this treatment is ready for application on a wider clinical basis (48,49).

One important final statement has to be made. Although the developments in chemical cholecystectomy are promising, chemical ablation of the gallbladder and cystic duct occlusion cannot rival cholecystectomy in one point: the prevention of gallbladder carcinoma. One can speculate that chemical obliteration of the gallbladder lumen may initiate an iatrogenic chronic gallbladder inflammation and therefore increase the likelihood of gallbladder carcinoma. Burhenne opposes this argument by stating that ablation of the gallbladder mucosa implies that no endothelium and no adenomatous rests remain. True gallbladder ablation would prevent subsequent occurrence of gallbladder carcinoma (43,50). At present, there are no data available to conclude that the risk on gallbladder carcinoma will increase or decrease after chemical ablation of the gallbladder.

6.3 Conclusions

We conclude that after successful dissolution therapy with oral bile acids without any further treatment recurrence of gallstones is inevitable in most patients. Reports of stone recurrence after ESWL, MTBE and other non-surgical gallbladder saving therapies are still too small and too short to draw any conclusion.

Prevention of stone recurrence (non-invasive or invasive) is still a challenge. The reports about low dose oral bile acids are contradictory and not very hopeful. NSAID's and HMG-CoA reductase inhibitors seem potentially good options to alter the biliary physiology in such a way as to prevent new stone formation. We believe that there is more future for chemical ablation of the gallbladder after cystic duct occlusion, which is a more definite solution to the recurrence problem. The success rate of this technique has to be improved and the long-term effects of gallbladder obliteration remain to be assessed before this technique can be accepted for clinical application following successful non-surgical gallbladder saving therapy for cholecystolithiasis.

6.4 References

1. Langenbuch C. Ein Fall von Extirpation der Gallenblase wegen chronischer Cholelithiasis. Heilung. Berliner Klin Wochenschr 1882; 19: 725-7.
2. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989; 158: 174-8.
3. Danzinger RG, Hofmann AF, Schoenfield LJ, Thistle JL. Dissolution of cholesterol gallstones by chenodeoxycholic acid. N Engl J Med 1972; 286: 1-8.
4. Podda M, Zuin M, Battezzati PM, Ghezzi C, de Fazio C, Dioguardi ML. Efficacy and safety of a combination of chenodeoxycholic acid and ursodeoxycholic acid for gallstone dissolution: a comparison with ursodeoxycholic acid alone. Gastroenterology 1989; 96: 222-9.
5. Schoenfield LJ, Lachin JM, the Steering Committee and the National Cooperative Gallstone Study Group. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone Study. A controlled trial of efficacy and safety. Ann Int Med 1981; 95: 257-82.
6. Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Rapid dissolution of gallstones by methyl tert-butyl ether. N Engl J Med 1985; 312: 217-20.
7. Sauerbruch T, Delius M, Paumgartner G, Holl J, Wess O, Weber W, Hepp W, Brendel W. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22.
8. Kellett MJ, Wickham JEA, Russell RCG. Percutaneous cholecystolithotomy. Br Med J 1988; 296: 453-5.
9. Miller FJ, Kensey KR, Nash JE. Experimental percutaneous gallstone lithotripsy: results in swine. Radiology 1989; 170: 985-7.
10. Thistle JL. Postdissolution gallstone recurrence. A clinical perspective. Dig Dis Sci 1989; 34: 44S-48S.
11. Villanova N, Bazzoli F, Taroni F, Frabboni R, Mazzella G, Festi D, Barbara L, Roda E. Gallstone recurrence after successful oral bile acid treatment. A 12-year follow-up study and evaluation of long-term postdissolution treatment. Gastroenterology 1989; 97: 726-31.
12. Ruppin DC, Dowling RH. Is recurrence inevitable after gallstone dissolution by bile-acid treatment? Lancet 1982; i: 181-5.
13. O'Donnell LDJ, Heaton KW. Recurrence and re-recurrence of gall stones after medical dissolution: a longterm follow up. Gut 1988; 29: 655-8.
14. Hood K, Ruppin DC, Gleeson D, Dowling RH. Prevention of gallstone recurrence by non-steroidal anti-inflammatory drugs. Lancet 1988; ii: 1223-5.
15. Leiss O, Bergmann K von. Rezidivprophylaxe nach erfolgter Gallensteinauflösung. Z Gastroenterol 1991; 29: 301-5.
16. Cooperberg PL, Burhenne HJ. Real-time ultrasonography: diagnostic technique of choice in calculous gallbladder disease. N Engl J Med 1980; 302: 1277-9.
17. Krook PM, Allen FH, Bush WH, et al. Comparison of real-time cholecystosonography and oral cholecystography. Radiology 1980; 135: 145-8.
18. Shapero TF, Rosen IE, Wilson SR, Fisher MM. Discrepancy between ultrasound and oral cholecystography in the assessment of gallstone dissolution. Hepatology 1982; 2: 587-90.
19. Lanzini A, Jazrawi RP, Kupfer RM, Maudgal DP, Joseph AEA, Northfield TC. Gallstone recurrence after medical dissolution. An overestimated threat? J Hepatol 1986; 3: 241-6.
20. Somerville KW, Rose DH, Bell GD, Ellis WR, Knapp DR. Gall-stone dissolution and recurrence: are we being misled? Br Med J 1982; 284: 1295-7.
21. Sackmann M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gallstone recurrence rate after successful shock-wave therapy. Gastroenterology 1990; 98: 392-6.

22. Scholz DG, McCullough JE, Petersen BT, Thistle JL. Gallstone recurrence following complete dissolution with oral bile acid therapy or methyl tert-butyl ether. Hepatology 1988; 8: 1372.
23. McCullough JE, Stadheim LM, Reading CC, Petersen BT, Thistle JL. Gallstone recurrence after methyl tert-butyl ether dissolution. Gastroenterology 1990; 98: A255.
24. Freeny PC, Feldman R. Long-term follow-up of patients treated with methyl tert-butyl ether for gallstone dissolution. Radiology 1990; 177(P): 90.
25. Chiverton SG, Inglis JA, Hudd C, Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy: the first 60 patients. Br Med J 1990; 300: 1310-2.
26. Norrby S, Schönebeck J. Long-term results with cholecystolithotomy. Acta Chir Scand 1970; 136: 711-3.
27. Pelletier G, Capdeville R, Mosnier H, et al. Low gallstone recurrence rate after successful lithotripsy in patients with solitary stones. Hepatology 1990; 12: 869.
28. Hood K, Gleeson D, Ruppin D, Dowling H. Can gallstone recurrence be prevented?: the Britsh/Belgian post-dissolution trial. Gastroenterology 1988; 94: A548.
29. Thistle JL, Yu PYS, Hofmann AF, Ott BJ. Prompt return of bile to supersaturated state followed by gallstone recurrence after discontinuance of chenodeoxycholic acid therapy. Gastroenterology 1974; 66: 789.
30. Marks JW, S Lan, the steering committee, and the national cooperative gallstone study group. Low-dose chenodiol to prevent gallstone recurrence after dissolution therapy. Ann Intern Med 1984; 100: 376-81.
31. Broomfield PH, Chopra R, Sheinbaum RC et al. Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. N Engl J Med 1988; 319: 1567-72.
32. Key PH, Bonorris GG, Marks JW, Chung A, Schoenfield LJ. Biliary lipid synthesisand secretion in gallstone patients before and during treatment with chenodeoxycholic acid. J Lab Clin Med 1980; 95: 816-26.
33. Bennion LJ, Grundy SM. Effects of obesity and caloric intake on biliary lipid metabolism in man. J Clin Invest 1975; 56: 996-1011.
34. Miettinen TA. Cholesterol production in obesity. Circulation 1971; 44: 842-50.
35. Hoogerbrugge-vd Linden N, deRooy FWM, Jansen H, van Blankenstein M. Effect of pravastatin on biliary lipid composition and bile acid synthesis in familial hypercholesterolemia. Gut 1990; 31: 348-50.
36. Mitchell JC, Stone BG, Logan GM, Duane WC. Role of cholesterolsynthesis in regulation of bile acid synthesis and biliary cholesterol secretion in man. J Lipid Res 1991; 32: 1143-9.
37. Logan GM, Duane WC. Lovastatin added to ursodeoxycholic acid further reduces biliary cholesterol saturation. Gastroenterology 1990; 98: 1572-6.
38. Salomonowitz E, Frick MP, Simmons RL. Obliteration of the gallbladder without former cholecystectomy. A feasibility study. Arch Surg 1984; 119: 725-9.
39. Remley KB, Cubberley DA, Watanabe AS, Nelson JA, Colby TV. Systemic absorption of gallbladder sclerosing agents in the rabbit. A preliminary study. Invest Radiol 1986; 21: 396-9.
40. Getrajdman GI, O'Toole K, Logerfo P, Laffey KJ, Martin EC. Transcatheter sclerosis of the gallbladder in rabbits: a preliminary study. Invest Radiol 1985; 20: 393-8.
41. Becker CD, Quenville NF, Burhenne HJ. Gallbladder ablation through radiologic intervention: an experimental alternative to cholecystectomy. Radiology 1989; 171: 235-40.
42. Brakel K, Laméris JS, Vergunst H, ten Kate FJW, Nijs HGT, Terpstra OT. Sclerotherapy of the gallbladder in pigs: development of a balloon catheter for a single-step procedure. Invest Radiol 1991; 26: 804-9.
43. Becker GJ, Kopecky KK. Can the newer interventional procedures replace cholecystectomy for cholecystolithiasis? The potential role of percutaneous cystic duct ablation. Radiology 1988; 167: 275-9.
44. Getrajdman GI, O'Toole K, Laffey KJ, Martin EC. Cystic duct occlusion and transcatheter sclerosis of the gallbladder in the rabbit. Invest Radiol 1986; 21: 400-3.

45. Leahy AL, McCollum PT, O'Gorman S et al. Cystic duct obliteration and gallbladder mucosal destruction: a feasible alternative to cholecystectomy. Br J Surg 1991; 78: 1321-4.

46. Saini S, Mueller PR, Girard M et al. Percutaneous ablation of the gallbladder : in vivo animal experiments. Radiology 1990; 177(P): 91.

47. Becker CD, Quenville NF, Burhenne HJ. Long-term occlusion of the porcine cystic duct by means of endoluminal radio-frequency electrocoagulation. Radiology 1988; 167: 63-8.

48. Becker CD, Fache JS, Malone DE, Stoller JL, Burhenne HJ. Ablation of the cystic duct and gallbladder: clinical observations. Radiology 1990; 176: 687-90.

49. Burhenne HJ, Lee SH, Fache JS, Stoller JL, Becker CD. Radiologic gallbladder ablation: two-year follow-up. Radiology 1990; 177(P): 90.

50. Burhenne HJ. Can the newer interventional procedures replace cholecystectomy for cholecystolithiasis? Radiology 1989; 170: 574-5.

CHAPTER 7

Extracorporeal Shock Wave Treatment of Common Bile Duct Stones: a Single Institution Experience with Two Different Lithotriptors

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Abstract

Extracorporeal shock wave lithotripsy (ESWL) is a new treatment modality for retained common bile duct (CBD) stones. Sixty-two patients (mean age 75 yr, range 27-95) with retained CBD stones were treated with two different lithotriptors. One of the lithotriptors operated on the electrohydraulic principle (Dornier HM-3 [n=13]), the other on the electromagnetic principle (Siemens Lithostar[R] [n=49]). All HM-3 patients were treated under general anaesthesia whereas with the Lithostar 1 patient was treated under general anaesthesia; 43 others received analgaesia and sedation and 5 had no analgaesia at all. Patients treated with the Lithostar had more sessions (mean 1.9 vs 1.3, $p<0.05$) and needed more shock waves (mean 8611 vs 2534, $p<0.001$) than patients treated with the HM-3. Fragmentation was achieved in all patients treated with the HM-3 and in 42 (86%) patients treated with the Lithostar. In this latter group 10 patients underwent a common bile duct exploration, without complications. Eleven patients had transient haematuria after treatment with the HM-3 and two patients (one in each group) had a subcapsular haematoma of the right kidney, all without clinical sequelae. At follow-up (median: HM-3 43 months, Lithostar 18 months), none of the patients had biliary complaints. We conclude that ESWL of retained CBD stones is safe and effective with both lithotriptors and should be considered before surgery in the elderly or high-risk patient.

Introduction

Clinical experience with extracorporeal shock wave lithotripsy (ESWL) for treatment of kidney stones was first reported in 1980 (1). ESWL is now the treatment of choice for urolithiasis and more than 500,000 patients with renal stones have been treated worldwide.

Since these satisfying results in urology, research have been done to enlarge the area of application of ESWL. Sauerbruch et al. reported in 1986 successful fragmentation of gallbladder- and common bile duct (CBD) stones by ESWL (2). It appeared that stones of different chemical composition could be disintegrated (3,4). Recently promising results of ESWL for pancreatic duct stones were reported (5-7), and the effects of high energy shock waves on tumour cells are being studied (8-11).

CBD stones can present either as the first sign of biliary stone disease or after cholecystectomy with or without exploration of the CBD. Surgical intervention by CBD exploration is an accepted therapy but has serious morbidity and mortality in the elderly or high-risk patient (12-14). Several less invasive alternatives for treatment of CBD stones have been developed. Endoscopic sphincterotomy and removal of the stones, with or without mechanical crushing with a Dormia basket, was introduced in 1972 and is nowadays the treatment of choice for elderly patients with CBD stones and prior cholecystectomy or for patients with an increased risk for surgery (15-17). Chemical dissolution with different solvents has been studied: ethylenediamine tetra-acetic acid (EDTA) (18), mono-octanoin (19,20), methyl *tert*-butyl ether (MTBE) (21) or orally administered bile acids (22) Other alternative invasive treatment modalities have also been studied: intracorporeal shock wave lithotripsy (23-26), laser lithotripsy (27-28), T-tube extraction (29,30), percutaneous transhepatic removal (31) but all these techniques are more cumbersome and less successful than endoscopic removal.

In approximately 10% of patients presenting to the endoscopist it is not possible to cannulate the sphincter of Oddi and remove the stones from the CBD (15). This can be due to a discrepancy between the diameter of the stone and that of the distal CBD, when there is a duodenal diverticulum, after Billroth-II gastric resection or after Roux-en-Y anastomosis. In these cases, especially in the high-risk patient, ESWL offers an attractive alternative to surgical exploration of the CBD. About 400 patients with CBD stones are reported to have been treated with ESWL, using either a first- or a second-generation lithotriptor (32-35). In this report we present a single institution experience with 62 consecutive patients with retained CBD stones, using a first-generation electrohydraulic- and a second-generation electromagnetic lithotriptor.

Patients and Methods

Patients

Inclusion criteria for ESWL-treatment in patients with CBD stones are summarised in Table 1.

1.	One or more symptoms of obstruction by CBD-stones (jaundice, abdominal pain, fever).
2.	Endoscopic extraction is impossible.
3.	Successful positioning of the patient on the lithotriptor and visualisation of (at least the most distal) stones by fluoroscopy after contrast injection.
4.	No lung tissue, cysts or abdominal aneurysms in the shock-wave pathway.
5.	No coagulopathy.
6.	No pregnancy.

Table 1. Inclusion criteria for extracorporeal shock wave lithotripsy (ESWL) of common bile duct (CBD) stones.

Patients treated with the Dornier HM-3 lithotriptor

Between April 1986 and July 1987 13 patients (12 females, 1 male) were treated for retained CBD stones using the Dornier HM-3 (Dornier Medizintechnik GmbH, Germering, FRG). Mean age was 79 yr (range 67-92 yr). Eleven patients had jaundice and 7 patients had cholangitis. Twelve patients had had previous endoscopic sphincterotomy and nasobiliary drainage. One patient was treated with percutaneous transhepatic biliary drainage because of a previous Billroth-II gastric resection. Four patients (31%) had had prior cholecystectomy.

Four patients had solitary stones, 4 had two stones and 5 patients had three or more stones. The diameter of the largest stone ranged from 20 to 52 mm (mean 29 mm). Two patients with CBD stones had intrahepatic stones as well.

Patients treated with the Siemens Lithostar lithotriptor.

From September 1987 till November 1990, 49 patients (26 women, 23 men) underwent ESWL for CBD calculi with the Siemens Lithostar[R] (Siemens AG, Erlangen, FRG). Mean age was 74 yr (range 27-95 yr). Seventeen patients suffered from abdominal pain, 19 patients had jaundice and 5 patients had cholangitis. Previous endoscopic sphincterotomy and insertion of a nasobiliary tube was performed in 36 patients. In four patients a Dormia-basket had remained impacted in the CBD after attempts at endoscopic removal of stones. Nine patients had a T-tube *in situ* and 4 patients had a percutaneous transhepatic catheter because endoscopy was impossible. In 17 patients the gallbladder was still *in situ*. Twenty-two patients (45%) had solitary stones, 13 (27%) had two stones and 14 (28%) had three or more stones. Mean diameter of the largest stone was 24 mm (range 10-50 mm). Six patients had, besides CBD stones, intrahepatic stones. Ten patients had retained stones after cholecystectomy with or without CBD exploration.

Shock wave treatment

Pretreatment investigations included: cholangiography, chest X-ray, white blood cell count (WBC), serum levels of bilirubin, liver enzymes, amylase and a coagulation profile.

With the HM-3 lithotriptor all patients were treated in the supine position under general anaesthesia with 'high-frequency jet ventilation' to diminish the hindrance of breath excursions on focussing the stones. In this way the stones remained as long as possible in the focal area of the shock waves. Because administration of the shock waves by the Lithostar caused less pain, only one of these patients needed general anaesthesia; 43 patients received analgaesia and sedation (usually intravenous fentanyl and midazolam) and 5 patients needed no analgaesia at all. None of the patients in this group got 'high-frequency jet ventilation'. With the Lithostar 44 patients were treated in the prone position, 2 in the supine position and 3 in the left lateral position.

In all patients the stones were visualized by fluoroscopy after injection of contrast material (Telebrix 38^{R}, Laboratoire Guerbet, Aulnay, France) into the CBD using either the nasobiliary drain, the postsurgical T-tube or the percutaneous transhepatic catheter. All treatments were performed under intravenous antibiotic prophylaxis (amoxycillin: 1 g intravenously, 1 hr before ESWL and 8, 16 and 24 hr thereafter and gentamicin 1.5 mg/kg body weight intravenously, 1 hr before ESWL and 8 and 16 hr thereafter).

The day after ESWL-treatment the fragmentation results were evaluated by cholangiography. If the remaining fragments were considered too large to be evacuated by either biliary drainage, endoscopic measures or percutaneous transhepatic procedures, another ESWL-session was carried out. Chest X-ray and ultrasound examination of the upper abdomen were carried out. WBC and serum levels of bilirubin, liver enzymes and amylase were determined. Biliary lavage with sterile water (4 L/24 hr) was started when fragmentation of the largest stone was observed at cholangiography. When total clearance of the CBD could not be achieved with biliary lavage, endoscopy or a percutaneous transhepatic procedure to extract the fragments was carried out.

Statistical evaluation of the data was performed by the Mann-Whitney U-test.

Results

Success rate

Dornier HM-3 group

Data of the treatments are given in Table 2. Ten patients had one session, 2 patients had two sessions and 1 patient had three sessions. The patients treated with the Lithostar had more treatment sessions ($p<0.05$) and needed more shock waves ($p<0.001$).

		HM-3 n=13	Lithostar n=49
average number of sessions		1.3 ± 0.2	1.9 ± 0.1 *
number of shock waves per session		1983 ± 170	4441 ± 116 **
number of shock waves per patient		2534 ± 513	8611 ± 693 **
		number of patients	
position:	supine	13	2
	prone	0	44
	left lateral	0	3
anaesthesia:	general	13	1
	IV-analgaesia and sedation	0	43
	none	0	5

Table 2. Treatment characteristics of Extracorporeal Shock Wave Lithotripsy of common bile duct stones. Values are given as mean ± SEM, *p < 0.05, **p < 0.001

Stone disintegration and clearance of the CBD was achieved in all patients (Fig. 1). In 3 patients the CBD was cleared of stone fragments with biliary lavage. Ten patients needed adjuvant intervention to clear the CBD; in 9 patients this was managed by endoscopic extraction of stone fragments. In one patient it was necessary to clear the CBD by a percutaneous transhepatic approach, because endoscopic extraction was impossible due to a previous Billroth-II gastric resection.

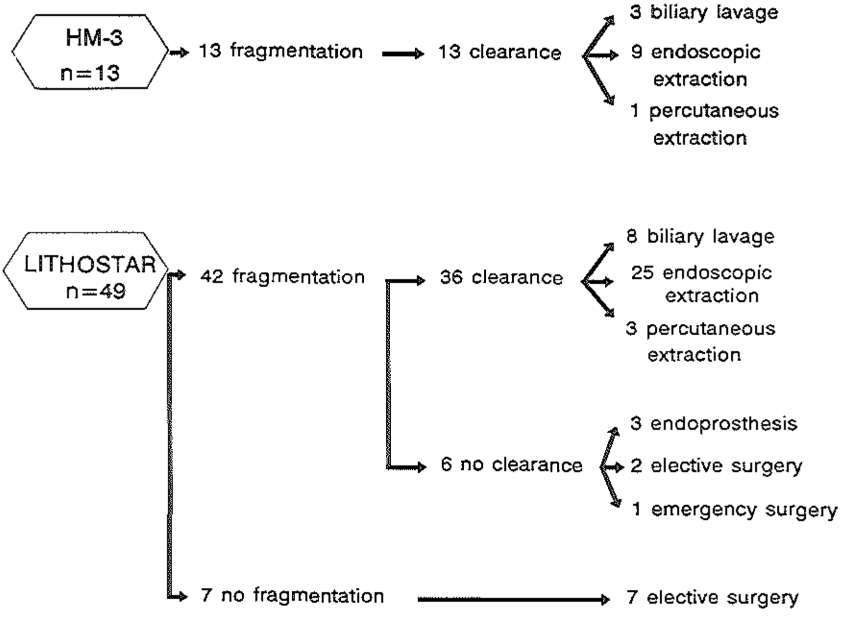

Figure 1. Results of Extracorporeal Shock Wave Lithotripsy of retained common bile duct stones using two different lithotriptors. HM-3 refers to Dornier HM-3, Lithostar refers to Siemens Lithostar[R].

In one patient one small stone remained in the right hepatic duct but it caused no bile obstruction or pain. None of the patients needed emergency surgery. Median hospitalisation time after the final ESWL-treatment was 14 days (range 4-26).

Siemens Lithostar group

Nineteen patients had one session, 16 patients had two sessions, 12 patients had three sessions and 2 patients had four sessions. In this group of 49 patients fragmentation of stones was achieved in 42 patients (86%). Stone clearance of the CBD was obtained in 36 patients (73%). Biliary lavage resulted in complete clearance of the CBD in 8 patients. Endoscopic removal of fragments was successful in 25 patients while 3 patients needed percutaneous transhepatic clearance of the bile ducts.

Total clearance of the CBD could not be obtained in 6 patients although fragmentation was observed at post-ESWL cholangiography. Endoscopic placement of an endoprosthesis, which was impossible prior to ESWL, was successfully achieved in 3 of these patients. The other 3 patients had a choledochotomy, 2 patients in an elective setting and in one patient emergency surgery was necessary. In this latter patient attempted endoscopic extraction of fragments in an impacted Dormia-basket was complicated by perforation of the CBD. Surgical exploration of the CBD, after cholecystectomy, showed fragmented stones in a perforated duct.

In 7 patients, in whom no fragmentation was achieved, an elective choledochotomy was carried out. Median hospitalisation time after the final ESWL-treatment was 16 days (range 1-76).

Complications and side effects

Eleven of the 13 patients treated with the HM-3 had transient macroscopic haematuria (among which one patient had a subcapsular haematoma of the right kidney), while none of the patients who underwent ESWL-treatment with the Lithostar had haematuria. In the Lithostar group one patient had a transient subcapsular haematoma of the right kidney as demonstrated with ultrasound imaging. Chest X-ray, one day after treatment, showed no abnormalities in both groups. Liver haematoma and pancreatitis were never observed. Sepsis, with positive blood cultures (Pseudomonas aeruginosa and Escherichia coli), occurred in 2 patients (one in each group). Sepsis resolved rapidly with antibiotic treatment (piperacillin and gentamicin) and intravenous plasma administration. There was no hospital mortality in both groups.

Serum levels before the first and after the final ESWL-treatment are presented in table 3. Bilirubin, ASAT and ALAT values decreased to nearly normal values. Mean gamma-GT and alkaline phosphatase values decreased also after ESWL but remained higher than the upper limit of the reference values.

Follow-up

Median follow-up time in the HM-3 group was 43 months (range 1-55). In this period 2 patients died of non-biliary causes. Two other patients were lost to follow-up, 1 and 4 months after the final ESWL-treatment without biliary symptoms or signs. The remaining 9 patients had no biliary problems since their final ESWL-treatment. Patients treated with the Lithostar had a median follow-up time of 18 months (range 2-37). In this group 4 patients died of non-biliary causes. None of these patients (including the patients who underwent surgery) had biliary symptoms or signs after their last treatment.

	HM-3 n=13		Lithostar n=49	
	pre-ESWL	post-ESWL §	pre-ESWL	post-ESWL §
WBC (4.0 - 10.0 x 10^9/L) ¥	9.5 (4.9-14.2)	6.8 * (4.1-9.7)	8.0 (3.9-31.4)	7.4 (4.2-11.4)
bilirubin (2 - 12 μmol/L)	36 (5 - 179)	13 * (4 - 48)	19 (6 - 203)	12 ** (5 - 65)
alkaline phosphatase (25 - 75 U/L)	194 (72 - 327)	113 (62 - 310)	178 (53 - 839)	126 ** (32 - 537)
gamma-GT (5 - 35 U/L)	110 (20 - 318)	94 (30 - 193)	130 (14 - 746)	67 ** (16 - 451)
ASAT (5 - 30 U/L)	53 (14 - 425)	24 (13 - 58)	27 (12 - 522)	26 (11 - 192)
ALAT (5 - 30 U/L)	64 (19 - 775)	26 (10 - 197)	34 (9 - 449)	25 * (6 - 196)
alpha-amylase (30 - 130 U/L)	97 (28 - 404)	70 (30 - 130)	86 (31 - 311)	105 (39 - 190)

Table 3. Laboratory findings before and after Extracorporeal Shock Wave Lithotripsy (ESWL) of common bile duct stones.

Values are presented as median with ranges in parentheses.
§ refers to values after the final ESWL-treatment.
¥ laboratory reference values.
* $p < 0.05$, ** $p < 0.01$ versus values before ESWL for either lithotriptor.

Discussion

Since the introduction of endoscopic sphincterotomy, treatment of common bile duct (CBD) stones has changed dramatically. At present, surgical choledochotomy is no longer always the therapy of choice due to the invasive character with associated morbidity and mortality. Extracorporeal shock wave lithotripsy (ESWL) offers a non-surgical alternative when endoscopic stone extraction fails.

We treated 62 consecutive patients with retained CBD stones with ESWL on two different lithotriptors, one lithotriptor using the electrohydraulic principle (Dornier HM-3 [n=13]), the other using an electromagnetic principle (Siemens Lithostar [n=49]). Stone clearance of the CBD, after the final ESWL-treatment, was achieved in 79% of the patients who otherwise would have been subjected to surgical CBD exploration. After fragmentation, stone clearance was achieved by biliary lavage in 11 patients, by endoscopy in 34 patients and by percutaneous transhepatic approach in 4 patients (36).

There are important differences between the two lithotriptors with regard to patient management. Firstly, patients in the HM-3 group were treated under general anaesthesia. Shock waves at maximal energy level caused too much pain to be controlled with intravenous analgaesia and sedation. General anaesthesia has the advantage that from the beginning of the treatment shock waves can be delivered at maximum energy level. We must emphasize that the Dornier HM-3 is a first generation lithotriptor (with waterbath). As others have demonstrated ESWL-treatment with the modified Dornier lithotriptor, without waterbath, is also possible without general anaesthesia (32). In patients treated with the Lithostar, pain caused by the shock waves could be managed satisfactorily by intravenous analgaesia and sedation. Use of this type of analgaesia implies that the generator voltage can only be gradually increased. Secondly, patients treated with the HM-3 had 'high-frequency jet ventilation' to diminish the breath excursions. With this type of artificial respiration the stones remained in the focal energy area of the shock waves as long as possible. Patients with intravenous analgaesia and sedation (Lithostar) are not suitable for 'high frequency jet ventilation'. Thirdly, patients with the HM-3 were treated in the supine position whereas most patients (44/49) with the Lithostar were treated in the prone position. Interposition of bowel gas presumably absorbs shock wave energy (37). This is more likely to occur in the prone than in the supine position.

Although the ultimate results, defined as fragmentation rate and CBD clearance, are comparable for these two lithotriptors, there exists a trade-off between the type of anaesthesia and the intensity of treatment. This results from the inherent differences in focal geometry of these two lithotriptors (38,39). The HM-3, at the 21 kV discharge potential, produces pressures up to 38.6 MPa in a focal area of 20 x 120 mm, whereas the Lithostar, at the 19.0 kV level, generates pressures up to 32.5 MPa in a focal area of 9 x 95 mm. Patients treated with the Lithostar needed more sessions and more shock waves per session but did not need general anaesthesia, which is an advantage in this relatively elderly high-risk population.

Regarding side-effects, transient macroscopic haematuria was frequently observed in the patients treated with the HM-3 lithotriptor. Two patients, one in each group, developed a subcapsular haematoma of the right kidney. Ultrasound imaging at follow-up showed complete disappearance of the haematomas within 4 and 6 days. Although these complications had no clinical sequelae, the long-term effects of such complications are unknown. Recently Williams et al. reported the long-term side effects of renal lithotripsy (40). Eight percent of the patients treated with ESWL for renal stones developed sustained hypertension after ESWL. Concern about these complications is necessary, because during ESWL-treatment of CBD-stones, shock waves may traverse the right kidney.

One patient in each group developed sepsis in spite of treatment under 24-hr antibiotic prophylaxis. However, these 2 patients also suffered from septic episodes prior to ESWL-treatment. Hence, there was no evident relation between the occurrence of sepsis and ESWL, ERCP or percutaneous transhepatic procedures.

We conclude that ESWL of CBD stones, after failed endoscopic extraction, offers several advantages over other non-operative therapies. It is a rapid, non-invasive, effective treatment with low complication rates and minimal discomfort for the patient. In our opinion extracorporeal shock wave lithotripsy of retained common bile duct stones should be considered before surgery in the elderly or high-risk patient.

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References

1. Chaussy Ch, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980; ii:1265-8.
2. Sauerbruch T, Delius M, Paumgartner G, Holl J, Wess O, Weber W, Hepp W, Brendel W. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22.
3. Terpstra OT, Lock MTWT, Blankenstein M van, Blijenberg BG, Dees J, Rating W, Schröder FH. In-vitro and in-vivo fragmentation of gallstones by extracorporeal shock waves. Eur Surg Res 1987; 19: 111-2.
4. Staritz M, Floth A, Rambow W, Göbel M, Mildenberger P, Meyer zum Büschenfelde KH. Shock wave lithotripsy of gallstones with second-generation device without conventional water bath. Lancet 1987; ii: 155.
5. Cremer M, Vandermeeren A, Delhaye M. Extracorporeal shock wave lithotripsy (ESWL) for pancreatic stones. Gastroenterology 1988; 94: A80.
6. Sauerbruch T, Holl J, Sackmann M, Paumgartner G. Extracorporeal shock wave lithotripsy of pancreatic stones. Gut 1989; 30: 1406-11.
7. Nijs HGT, Toom R den, Blankenstein M van, Schröder FH, Terpstra OT. Extracorporeal shock wave lithotripsy of pancreatic duct stones. Gut 1990; 31: 589-90A.
8. Russo P, Stephenson RA, Mies C et al. High energy shock waves suppress tumor growth in vitro and in vivo. J Urol 1986; 135: 626-8.
9. Russo P, Mies C, Huryk R, Heston WDW, Fair WR. Histopathologic and ultrastructural correlates of tumor growth suppression by high energy shock waves. J Urol 1987; 137: 338-41.
10. Goetz AE, Königsberger R, Gamarra F et al. Shockwave induced collapse of the tumor microcirculation: intravital microscopy (IM) and magnetic resonance imaging (MRI). Eur Surg Res 1988; 20(suppl 1): 118.
11. Dongen van JW, Steenbrugge GJ van, Romijn JC, Schröder FH. The cytocidal effect of high energy shock waves on human prostatic tumour cell lines. Eur J Cancer Clin Oncol 1989; 25: 1173-9.
12. McSherry CK, Glenn F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. Ann Surg 1980; 191: 271-5.
13. Doyle PJ, Ward-McQuaid JN, McEwen Smith A. The value of routine peroperative cholangiography - a report of 4000 cholecystectomies. Br J Surg 1982; 69: 617-9.
14. Braun L. Zum Risiko operativer Eingriffe an Gallenblase und Gallenwegen. Chirurg 1987; 58: 413-7.
15. Cotton PB. Endoscopic management of bile duct stones; (apples and oranges). Gut 1984; 25: 587-97.
16. Johnson AG, Hosking SW. Appraisal of the management of bile duct stones. Br J Surg 1987; 74: 555-60.
17. Martin DF, Tweedle DEF. Endoscopic management of common duct stones without cholecystectomy. Br J Surg 1987; 74: 209-11.
18. Leuschner U, Wurbs D, Baumgartel H, Helm EB, Classen M. Alternating treatment of common bile duct stones with a modified glyceril-1-monooctanoate preparation and a bile acid-EDTA solution by nasobiliary tube. Scand J Gastroenterol 1981; 16: 497-503.
19. Palmer KR, Hofmann AF. Intraductal mono-octanoin for the direct dissolution of bile duct stones: experience in 343 patients. Gut 1986; 27: 196-202.
20. Jarrett LN, Bell GD, Balfour TW, Knapp DR, Rose DH. Intraductal infusion of mono-octanoin: experience in 24 patients with retained common-duct stones. Lancet 1981; i: 68-70.
21. Murray WR, Laferla G, Fullarton GM. Choledocholithiasis-in vivo stone dissolution using methyl tertiary butyl ether (MTBE). Gut 1988; 29: 143-5.
22. Salvioli G, Salati R, Lugli R, Zanni C. Medical treatment of biliary duct stones: effect of ursodeoxycholic acid administration. Gut 1983; 24: 609-14.
23. Burhenne HJ. Electrohydrolytic fragmentation of retained common duct stones. Radiology 1975; 117: 721-2.

24. Lear JL, Ring EA, Macoviak JA, Baum S. Percutaneous transhepatic electrohydraulic lithotripsy. Radiology 1984; 150: 589-90.

25. Hwang MH, Yang JC, Lin J. The treatment of retained intrahepatic stones with electrohydraulic and ultrasonic shock waves. Dig Dis Sci 1986; 31: 10.

26. Liguory CL, Bonnel D, Canard JM, Cornud F, Dumont JL. Intracorporeal electrohydraulic shock wave lithotripsy of common bile duct stones: preliminary results in 7 cases. Endoscopy 1987; 19: 237-40.

27. Orii K, Ozaki A, Takase Y, Iwasaki Y. Lithotomy of intrahepatic and choledochal stones with YAG laser. SGO 1983; 156: 485-8.

28. Ell Ch, Lux G, Hochberger J, Müller D, Demling L. Laserlithotripsy of common bile duct stones. Gut 1988; 29: 746-51.

29. Burhenne HJ. Percutaneous extraction of retained biliary tract stones: 661 patients. AJR 1980; 134: 888-98.

30. Chen MF, Chou FF, Wang CS, Jang YI. Experience with and complications of postoperative choledochofiberscopy for retained biliary stones. Acta Chir Scand 1982; 148: 503-9.

31. Clouse ME, Stokes KR, Lee RGL, Falchuk KR. Bile duct stones: percutaneous transhepatic removal. Radiology 1986; 160: 525-9.

32. Sauerbruch T, Stern M. Fragmentation of bile duct stones by extracorporeal shock waves. A new approach to biliary calculi after failure of routine endoscopic measures. Gastroenterology 1989; 96: 146-52.

33. Bland KI, Jones RS, Maher JW et al. Extracorporeal shock-wave lithotripsy of bile duct calculi. Ann Surg 1989; 209: 743-55.

34. Vergunst H, Terpstra OT, Brakel K, Laméris JS, Blankenstein M van, Schröder FH. Extracorporeal shockwave lithotripsy of gallstones. Possibilities and limitations. Ann Surg 1989; 210: 565-75.

35. Staritz M, Rambow A, Grosse A. Electromagnetically generated extracorporeal shockwaves for fragmentation of extra- and intrahepatic bile duct stones: indications, success and problems during a 15 months clinical experience. Gut 1990; 31: 222-5.

36. Groen JN, Lock MTWT, Laméris JS, Blankenstein M van, Terpstra OT. Removal of common bile duct stones by the combination of percutaneous balloon dilatation and extracorporeal shock wave lithotripsy. Gastroenterology 1989; 97: 202-6.

37. Staritz M, Rambow A, Bork K, Thelen M, Hohenfellner R, Meyer zum Büschenfelde KH. Second generation extracorporeal shock waves for therapy of selected bile duct stones: 18 months of clinical experience. Gastroenterology 1988; 94: A 594.

38. Vergunst H, Terpstra OT, Schröder FH, Matura E. Assessment of shock wave pressure profiles in vitro: clinical implications. J Lithotripsy Stone Dis 1989; 1: 289-98.

39. Coleman AJ, Saunders JE, Preston RC, Bacon DR. Pressure waveforms generated by a Dornier extracorporeal shock-wave lithotriptor. Ultrasound Med Biol 1987; 13: 651-7.

40. Williams CM, Kaude JV, Newman RC, Peterson JC, Thomas WC. Extracorporeal shock wave lithotripsy: long-term complications. AJR 1988; 150: 311-5.

CHAPTER 8

Extracorporeal Shock Wave Lithotripsy of Pancreatic Duct Stones

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Abstract

Chronic calcifying pancreatitis presents a major clinical problem, often requiring extensive surgery. Extracorporeal shock wave lithotripsy (ESWL) offers a new therapeutic option. We applied ESWL after endoscopic sphincterotomy of the pancreatic orifice in 8 patients with impacted pancreatic duct stones. An electromagnetic lithotriptor (Siemens Lithostar[R], Erlangen, FRG) was used. Patients were treated in prone position under fluoroscopic control. A mean of 6813 shock waves (range 1500-10000) was delivered in one or two sessions. Disintegration of stones was achieved in 6/8 patients, initial relief of pain in 7/8 patients and total clearance of the pancreatic duct in 3/8 patients. One patient had an exacerbation of her pancreatitis one day after ESWL, which resolved rapidly with medical treatment. No other complications were observed. Four/five patients with fragmented stones had no abdominal complaints at follow-up (mean 17 months, range 3-27). Three patients in whom ESWL was not completely successful (2 without and 1 with partial fragmentation) underwent an operation according to Puestow. Two of them still have abdominal complaints after surgery. From these data we conclude that ESWL of pancreatic duct stones is a promising new alternative for surgery, when endoscopic stone extraction fails.

Introduction

Treatment of chronic calcifying pancreatitis (CCP) forms a major clinical problem often requiring extensive surgery. Alcohol consumption is considered to be the main cause of CCP. About 90 % of these patients develop pancreatic lithiasis (1). The purpose of treatment of CCP is relief of pain, drainage of pancreatic pseudocysts and/or management of biliary obstruction.

When stones are present in the main pancreatic duct, endoscopic stone extraction, after sphincterotomy of the pancreatic orifice, is the treatment of choice. However this is often impossible, mostly due to discrepancy between the diameter of the stone and the diameter of the distal pancreatic duct or because previous gastric surgery makes endoscopic access to the sphincter of Oddi impossible. After failure of endoscopic measures these patients would often be treated by surgery. However, the morbidity and mortality after surgery for CCP vary between 20-40 % and 2-5 %, respectively (2).

After good results with extracorporeal shock wave lithotripsy (ESWL) for common bile duct stones, we were encouraged to apply ESWL in patients with pancreatic duct stones in whom endoscopic stone extraction had failed. In this paper we present the Rotterdam experience with ESWL in 8 patients with pancreatic duct stones.

Patients and Methods

Patients

From June 1988 till July 1990 we applied ESWL in 8 patients with pancreatic duct stones using the Siemens Lithostar[R] (Siemens AG, Erlangen, FRG). This second generation lithotriptor operates on an electromagnetical shock wave generation principle.

Characteristics of the 8 patients are presented in Table 1. All patients suffered from recurrent attacks of abdominal pain and had undergone endoscopic pancreatic sphincterotomy. Before applying ESWL to these patients we ensured that there was no acute cholecystitis, jaundice, cholangitis, acute pancreatitis or concomitant common bile duct stones.

Patient gender/age(yr)	serum amylase pre-ESWL (U/L)*	number of stones	diameter largest stone (mm)	alcohol abusus
A male/44	127	1	12	yes
B female/55	249	1	30	yes
C female/47	243	2	15	no
D male/41	382	2	30	yes
E female/37	73	>3	25	yes
F male/48	94	1	16	yes
G female/22	134	2	20	no
H female/43	126	>3	18	no

Table 1. Characteristics of 8 patients treated by extracorporeal shock wave lithotripsy for pancreatic duct stones.
* reference values: 30-130 U/L.

Methods

Pretreatment investigations included: chest X-ray, endoscopic retrograde cholangiopancreatography (ERCP), plain abdominal X-ray, white blood cells count (WBC), hemoglobin, serum levels of amylase, bilirubin, liver enzymes (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltranspeptidase) and a coagulation profile (prothrombin time, fibrinogen levels). All patients were treated in prone position under 24-hr antibiotic prophylaxis (gentamicin and amoxycillin).

Stones were visualized in all patients by fluoroscopy without contrast medium. When there was more than one stone the shock waves were focussed on the stone which was most likely to cause obstruction, usually this is the most distally located stone. When the vertebral column was in the shock wave path this was avoided by slight elevation of the patient's right hip. One patient was treated under general anesthesia, six had intravenous analgo-sedation (midazolam, fentanyl) and one patient needed no analgesia at all. The shock waves were delivered at a mean power output of 18.8 kV (range 17.2-19.0 kV).

Patient	number of sessions	total number of shock waves	fragmentation	clearance of pancreatic duct	serum amylase post-ESWL (U/L)*
A	2	8,000	no	no	138
B	2	10,000	yes	yes	93
C	2	6,000	yes	no	163
D	1	3,000	yes	yes	97
E	1	1,500	no	no	94
F	2	10,000	yes	yes	272
G	1	8,000	yes	no	132
H	2	8,000	yes	no	201

Table 2. Characteristics of extracorporeal shock wave treatments in 8 patients with pancreatic duct stones.
* reference values: 30-130 U/L.

The day after ESWL a plain abdominal X-ray was made and WBC, serum amylase, bilirubin and liver enzymes were determined. When no fragmentation was observed on the abdominal X-ray, a second ESWL was performed. When there was more than 50% disintegration of the stone on plain abdominal X-ray a new endoscopic attempt to extract the fragments was carried out.

Statistical evaluation of laboratory data was performed by the Mann-Whitney U-test.

Patient	follow-up after first ESWL (mo)	time between ESWL and operation (mo)	operative procedures	abdominal complaints at follow-up
A	27	7	Puestow	yes
B	22	-	-	no
C	20	13	Puestow	no
D	19	-	-	no
E	17	1,4,5	Puestow 2 relaparotomies	yes
F	12	-	-	no
G	12	-	-	no
H	3	-	-	yes

Table 3. Results of extracorporeal shock wave lithotripsy in 8 patients with pancreatic duct stones.

Results

Treatment characteristics are presented in Table 2. Serum amylase levels, one day after ESWL, dropped to 149±22 U/L [normal values 30-130 U/L] which was statistically not significant when compared to pre-treatment levels. ESWL resulted in stone disintegration in 6 patients. Initially relief of pain was obtained in 7 patients. Total clearance of the pancreatic duct was achieved in 3 patients. The pancreatic duct cleared spontaneously in one patient whereas in the other two patients the duct was cleared after lavage with sterilized water (2L/24hr) through a nasopancreatic tube which was endoscopically placed after ESWL. Fragmentation of the stones in three other patients did not result in a total clearance of the pancreatic duct, in spite of endoscopic attempts following ESWL. However there was a dramatic relief of abdominal pain attacks in these patients. Five/six patients with fragmented stones had no abdominal complaints at follow-up (mean 17 months, range 3-27) (Table 3). ESWL did not result in stone fragmentation in two patients. Three patients, two without fragmentation of the stones, one with a partially fragmented stone, remained suffering from abdominal pain attacks and had an operation according to Puestow (1,7 and 13 months after ESWL). One patient was initially free of abdominal pain attacks but still has chronic abdominal pain at 22 months follow-up. One of these patients was reoperated five months later and underwent a partial pancreatectomy and choledocho-duodenostomy. The patient is now at 12 months after the last operation and still suffering of abdominal pain attacks. The third patient is free of symptoms 8 months after surgery.

One patient, in whom stone fragmentation was achieved, had an exacerbation of her pancreatitis immediately after ESWL. There was no fever but serum amylase increased to 3760 U/l and WBC to 13.6 x 10^9/L (normal values up to 10 x 10^9/L). Serum bilirubin and liver enzymes remained in the normal range. The pancreatitis resolved rapidly with medical management in three days and this patient was discharged in good condition 7 days after ESWL. No other complications were observed after ESWL.

Case history

As a typical example, we present the following case history. A 41-year old man, known with alcohol abuse for more than 15 years and chronic calcifying pancreatitis since 5 years, suffered from recurrent attacks of epigastric pain. He had undergone multiple endoscopies with sphincterotomy of the pancreatic orifice which mostly resulted in temporary relief of pain. This time he was admitted to the hospital with severe epigastric pain. There was no fever. Serum amylase was elevated threefold. Liver enzymes, bilirubin, fasting glucose and white blood cells count were normal. A plain abdominal film showed a large solitary stone (diameter 30 mm) in the pancreatic region (fig. 1). After endoscopic stone extraction failed, one ESWL-treatment was carried out. Visualization of the stone was effected by

Figure 1. Plain abdominal X-ray before extracorporeal shock wave lithotripsy showing one large stone (arrow) in the main pancreatic duct (determined before ESWL at ERCP).

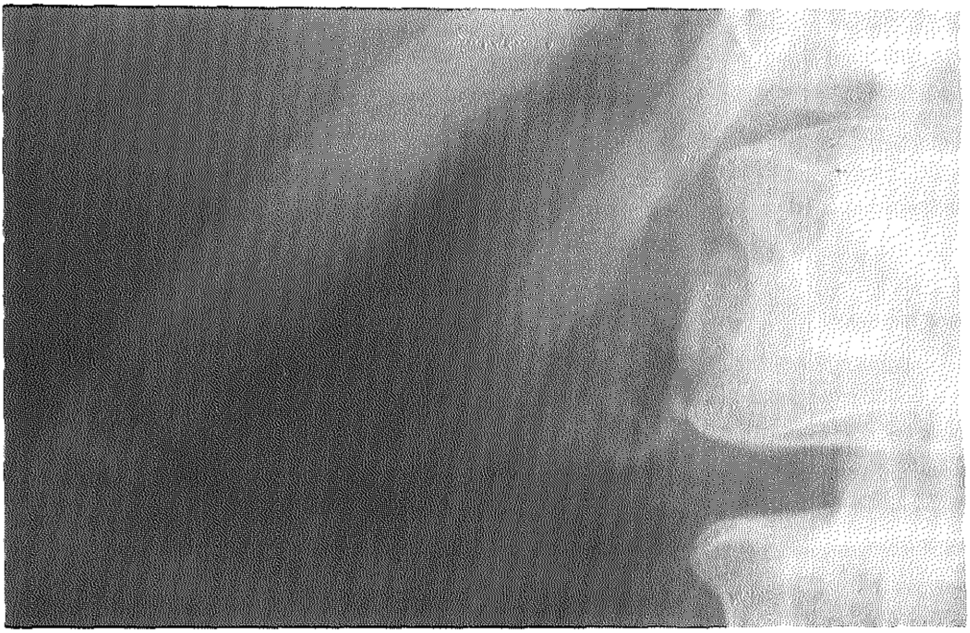


Figure 2. Plain abdominal X-ray after one extracorporeal shock wave lithotripsy session showing total clearance of the pancreatic duct (confirmed at ERCP post ESWL).

fluoroscopy without contrast medium. Three-thousand shock waves were delivered under intravenous analgo-sedation (fentanyl, midazolam). Adequate fragmentation of the stone was observed on a plain abdominal film one day after ESWL (fig. 2). There were no complications of ESWL and the serum amylase level dropped to normal values. The patient was discharged in a good condition six days after ESWL. At 20 months follow-up he had no abdominal complaints and at ERCP no stones could be detected in the main pancreatic duct.

Discussion

The indications for treatment of chronic calcifying pancreatitis (CCP) are severe abdominal pain, biliary obstruction and/or the existence of pseudocysts (3). The origin of pain in patients with CCP is still unclear. Dilatation of the pancreatic duct and existence of pseudocysts are possible causes of abdominal pain (1). The results of longitudinal pancreaticojejunostomy are satisfactory for pain relief when there is a dilated duct (3). Drainage of pseudocysts gives also good results for pain relief (1). Because the surgical treatment of CCP is associated with a notable morbidity and mortality, the application of alternative nonsurgical treatments are examined. Endoscopic sphincterotomy of the pancreatic duct orifice and extraction of stones or placing an endoprosthesis has a lower morbidity and mortality than surgery. However, it is often not possible to cut the pancreatic sphincter and/or extract the stones in all patients.

Since Chaussy et al. introduced extracorporeal shock wave lithotripsy (ESWL) in the treatment of kidney stones, the area of application of shock wave therapy has been enlarged (5). At present, also stones in the gallbladder, in the bile ducts and in the pancreatic duct are treated with ESWL (6-10).

We applied ESWL to 8 patients with pancreatic duct stones using the Siemens Lithostar^{R}, a lithotriptor which operates on the electromagnetical shock wave generation principle. Fragmentation was achieved in 6 patients, total clearance of the pancreatic duct was achieved in 3 patients. Spontaneous migration of fragments occurred in one patient and in two patients the fragments were rinsed out of the pancreatic duct by lavage through a endoscopically placed nasopancreatic tube which was placed after ESWL. Disintegration of the stones, but no total clearance of the pancreatic duct, was achieved in 3 patients whereas in 2 patients no fragmentation could be obtained. All patients but one with fragmented stones had a dramatic relief of pain after ESWL. Sauerbruch et al. found total relief of pain in 3/8 patients, two with total clearance of the pancreatic duct, one with fragmentation but no total clearance of stones. In 2/8 patients they achieved total clearance of the pancreatic duct but these patients remained suffering from abdominal pain attacks (8). Our findings are in accordance with Cremer et al., who reported relief of pain in patients in whom clearance of the pancreatic duct was achieved (9). Relief of pain could be due to diminution of the intraductal pressure in the pancreatic ducts through improved drainage.

ESWL was complicated in one patient by an exacerbation of pancreatitis which resolved rapidly with medical management. Whether this complication is due to migration of fragments through the pancreatic duct with subsequent obstruction or to direct damage of shock waves to the pancreatic tissue is not known. No other complications were observed.

Although ESWL is only of use in cases where calcified pancreatic stones cause obstruction of the main pancreatic duct it offers several advantages over surgery: it is less invasive and there is no need for general anaesthesia. ESWL is followed by less complications and requires only a short hospital stay. Also ESWL can be applied after pancreatic surgery when stone formation recurs.

The experience with ESWL in the treatment of pancreatic stones is still limited but the first results are promising. We conclude that after failed endoscopic extraction of pancreatic duct stones ESWL should be considered before surgery is undertaken, especially in the high risk patient.

References

1. Amman RW, Akovbiantz A, Largiader F, et al. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. Gastroenterology 1984; 86: 820-8.
2. Prinz RA, Greenlee HB. Pancreatic duct drainage in 100 patients with chronic pancreatitis. Ann Surg 1981; 194: 313-20.
3. Brinton MH, Pellegrini CA, Stein SF, et al. Surgical treatment of chronic pancreatitis. Am J Surg 1984; 148: 754-9.
4. Ammann RW, Münch R, Otto R, et al. Evolution and regression of pancreatic calcification in chronic pancreatitis. Gastroenterology 1988; 95: 1018-28.
5. Chaussy Ch, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980; ii: 1265-8.
6. Sackmann M, Delius M, Sauerbruch T et al. Shock wave lithotripsy of gallbladder stones. The first 175 patients. N Eng J Med 1988; 318: 393-7.
7. Sauerbruch T, Stern M. Fragmentation of bile duct stones by extracorporeal shock waves. Gastroenterology 1989; 96: 146-52.
8. Sauerbruch T, Holl J, Sackmann M, et al. Extracorporeal shock wave lithotripsy of pancreatic stones. Gut 1989; 30: 1406-11.
9. Cremer M, Vandermeeren A, Delhaye M. Extracorporeal shock wave lithotripsy for pancreatic stones. Gastroenterology 1988; 94: A80.
10. Nijs HGT, Toom R den, Blankenstein M van, et al. Extracorporeal shock wave lithotripsy of pancreatic duct stones. Gut 1990; 31: A589-90.

CHAPTER 9

General Discussion and Summary

Cholecystectomy for symptomatic gallbladder stones is effective, but morbidity (3-15%), mortality (0-5%) and costs stimulated research into non-operative treatment modalities (1-3). The treatment of gallbladder stones changed after the introduction of oral bile acids in 1972 (4). Hereafter several other alternative therapies to the "classic" cholecystectomy have been developed (5-9). The studies described in this thesis are all in the area of non-surgical management of biliary stones.

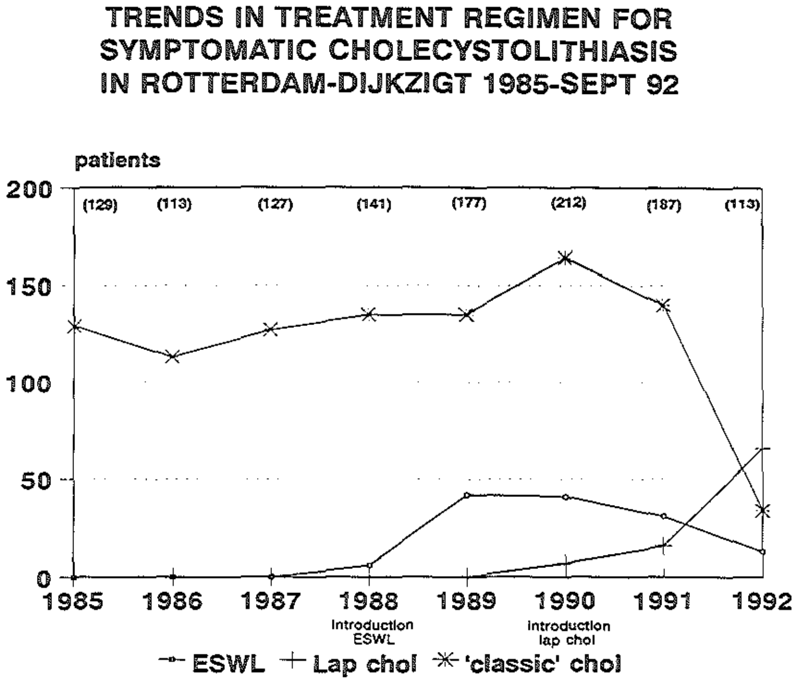


Figure 1.Trends in treatment regimen for symptomatic cholecystolithiasis in the University Hospital 'Dijkzigt' Rotterdam (1985-1992). Total number of patients treated for cholecystolithiasis in parentheses. ESWL=extracorporeal shock wave lithotripsy; lap chol=laparoscopic cholecystectomy; 'classic' chol=acute and elective 'classic' cholecystectomy.

The clinical introduction of extracorporeal shock wave lithotripsy (ESWL) in 1980 has dramatically changed the treatment regimen of kidney stones (10.) Surgical treatment for urolithiasis, which was the only option, is now restricted to less than 5% of all patients (11). Since these fascinating results were published, research has increased the clinical applicability of ESWL. After efficacy and safety studies in animals were carried out, ESWL is now clinically applied in the treatment of stones in the gallbladder, intra and extrahepatic bile duct, pancreatic duct, and salivary gland (12-16). Especially the introduction of ESWL in 1985 for the treatment of gallbladder stones and later the introduction of laparoscopic cholecystectomy in 1987 have had a major impact on the treatment regimen of cholecystolithiasis. Figure 1 represents the shifts of the treatments for cholecystolithiasis performed during the last 7 years in the University Hospital 'Dijkzigt' Rotterdam (introduction ESWL 1988, introduction laparoscopic cholecystectomy 1990). The number of cholecystectomies showed a slight increase in 1990. This was probably due to the start of our gallstone outpatient clinic in 1989, which increased the total number of admitted patients with gallbladder stones. In 1992 the number of 'open' cholecystectomies has dramatically decreased as did the number of ESWL treatments, when laparoscopic cholecystectomy became the therapy of choice for symptomatic gallbladder stones in our hospital.

ESWL for gallbladder stones has not succeeded in meeting the high expectations which emerged after the first very successful publications (17,18). We conclude that ESWL for symptomatic gallbladder stones, and adjuvant treatment with oral bile acids, is safe and relatively effective for a highly selective group of patients and should be reserved for high-risk patients or for patients who refuse surgery as a therapeutic option (Chapter 2).

To treat the fragments which remain after ESWL, we investigated the effect of combined ESWL and local contact dissolution with methyl *tert*-butyl ether (MTBE). This was very effective in an in vitro model leaving no fragments or grit after treatment. A feasibility study in a pig model failed to achieve fragmentation. This was most certainly due to inadequate ultrasound visualization of the stones after MTBE instillation. We demonstrated that simultaneous treatment with ESWL and MTBE did not result in extra tissue damage. Further studies are warranted to improve the localization technique for this combination treatment (Chapter 3).

Ultrasound plays an important role in monitoring the results of ESWL for gallbladder stones. The results of ultrasound after ESWL were analyzed and related to the results of ESWL. It was concluded that ultrasound has some limitations in assessing the efficacy of ESWL. Ultrasound influenced the clinical strategy in two ways: overestimation of efficacy by incorrectly demonstrating no fragments and underestimation of the fragment size which resulted in delay in retreatment with ESWL. Therefore a second (verification) ultrasound is advised if ultrasonographic examination reveals no fragments or fragments smaller than 5 mm before the treatment regimen is altered (Chapter 4).

We have studied the eligibility percentages for seven therapeutic modalities (i.e. cholecystectomy, laparoscopic cholecystectomy, oral bile acids, methyl *tert*-butyl ether, extracorporeal shock wave lithotripsy, percutaneous cholecystolithotomy, and rotary contact lithotripsy) based on the results of an analysis of almost 700 patients visiting our gallstone outpatient clinic. The eligibility percentages were highest for operative management of gallbladder stones (86-97%), and lowest for ESWL (18%). Regarding these percentages, the success percentages, the complication rate and the risk of stone recurrence, it is our opinion that at this moment laparoscopic cholecystectomy is the best treatment available for patients without an increased risk for surgery. Moreover we think that there will remain a place for non-operative treatments, especially for high-risk patients or when patients refuse surgery as a therapeutic option (Chapter 5).

A disadvantage of all gallbladder saving therapies is the risk of stone recurrence because the gallbladder remains *in situ*. We reviewed the literature and found that recurrence of gallbladder stones is inevitable in most patients when no further treatment is given after successful gallbladder saving treatment. Percentages of stone recurrence of up to 80% have been reported (19). Medical prevention of stone recurrence has not been successful so far but most of the studies are preliminary ones. Cystic duct occlusion and chemical sclerosis of the gallbladder is still in its infancy but the first results are promising. However the technique will have to be improved to make this a serious alternative to surgical cholecystectomy (Chapter 6).

Surgery for common bile duct stones is an accepted therapy but has serious morbidity and mortality percentages, especially in elderly patients. Therefore endoscopic stone extraction after papillotomy (which is possible in about 90% of the patients) is the therapy of choice. ESWL of common bile duct stones is an effective and safe therapy and we think that it has to be considered before surgery when endoscopic stone extraction is not possible. In most of our patients it was necessary to perform an additional treatment after ESWL (biliary lavage, endoscopy, or percutaneous transhepatically procedures) to achieve total fragment clearance (Chapter 7).

Chronic calcifying pancreatitis, which is mainly due to alcohol abuse, presents a major clinical problem. Endoscopic treatment and surgery have low success rates and a high morbidity and mortality rate. Therefore we studied the applicability of ESWL in the treatment of pancreatic duct stones. ESWL of pancreatic duct stones is a safe therapy with satisfactory results. Surprisingly it was not necessary to achieve a total clearance of the pancreatic duct for relief of abdominal symptoms of the pancreatic stones. However the follow-up is too short and the number of patients too small to make any definite conclusions (Chapter 8).

Epilogue

Summarizing the results it is our opinion that there will remain a place for ESWL in the treatment of gallstone disease. For patients with symptomatic gallbladder stones laparoscopic cholecystectomy will emerge as the therapy of choice and that ESWL should be reserved for patients who are unfit for surgery or when patients refuse surgery as a therapeutical option. ESWL for bile duct and pancreatic duct stones is the first treatment option for the elderly in whom endoscopic stone extraction has failed. We agree with Zeman et al. that ESWL has to be concentrated in centers where ESWL for kidney, gallbladder , bile duct, and pancreatic duct stones is carried out. On the one hand multidisciplinary teams for lithotripsy will become experienced whereas on the other hand the equipment cost can be justified (20).

Finally, a few words on the future application of shock waves in medicine, other than in gallstone and kidney stones. The first reports on ESWL for salivary gland stones seem promising (16,21). The role of ESWL in the treatment of malignities is still premature and experimental. Therefore no predictions for the future of this application can be made (22-25). The latest development in the area of ESWL is the application of extracorporeal shock waves in the treatment of hypertrophic pseudarthrosis. This seems to be a promising alternative to surgical therapy (26-27).

Although it cannot be foreseen what the ultimate role of ESWL in the management of patients with surgically curable disease will be, it has however grown into a powerful new tool in the surgical armamentarium just as the scalpel and the laser beam.

References

1. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989; 158: 174-8.
2. Meijer WS. Galblaasextirpaties in Nederland; frequentie, operatieve sterfte en postoperatieve complicaties (1987-1989). Ned Tijdschr Geneeskd 1991; 135: 1688-91.
3. Davies MG, O'Broin E, Mannion C et al. Audit of open cholecystectomy in a district general hospital. Br J Surg 1992; 79: 314-6.
4. Danzinger RG, Hofmann AF, Schoenfield LJ, Thistle JL. Dissolution of cholesterol gallstones by chenodeoxycholic acid. N Engl J Med 1972; 286: 1-8.
5. Sauerbruch T, Delius M, Paumgartner G, Holl J, Wess O, Weber W, Hepp W, Brendel W. Fragmentation of gallstones by extracorporeal shock waves. N Engl J Med 1986; 314: 818-22.
6. Allen MJ, Borody TJ, Bugliosi TF, May GR, LaRusso NF, Thistle JL. Rapid dissolution of gallstones by methyl tert-butyl ether. N Engl J Med 1985; 312: 217-20.
7. Kellett MJ, Wickham JEA, Russell RCG. Percutaneous cholecystolithotomy. Br Med J 1988; 296: 453-5.
8. Miller FJ, Kensey KR, Nash JE. Experimental percutaneous gallstone lithotripsy: results in swine. Radiology 1989; 170: 985-7.
9. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. Preliminary report of 36 cases. Ann Surg 1990; 211: 60-2.
10. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980; ii: 1265-8.
11. Chaussy C, Fuchs GJ. Current state and future developments of noninvasive treatment of human urinary stones with extracorporeal shock wave lithotripsy. J Urol 1989; 141: 782-9.
12. Vergunst H, Terpstra OT, Brakel K, Nijs HGT, Laméris JS, Kate FJW ten, Schröder FH. Biliary extracorporeal shockwave lithotripsy: short-term and long-term observations in an animal model. Submitted for publication.
13. Toom R den, Vergunst H, Nijs HGT, Brakel K, Laméris JS, Terpstra OT. Electromagnetic shock wave lithotripsy of gallbladder stones using a wide range of inclusion criteria. Am J Gastroenterol 1992; 87: 498-503.
14. Toom R den, Nijs HGT, Blankenstein M van, Laméris JS, Schröder FH, Terpstra OT. Extracorporeal shock wave treatment of common bile duct stones: experience with two different lithotriptors at a single institution. Br J Surg 1991; 78: 809-13.
15. Toom R den, Nijs HGT, Blankenstein M van, Schröder FH, Jeekel J, Terpstra OT. Extracorporeal shock wave lithotripsy of pancreatic duct stones. Am J Gastroenterol 1991; 86: 1033-6.
16. Iro H, Nitsche N, Waitz G, Schneider T, Benninger J, Ell C. Extracorporeal piezoelectric shock wave lithotripsy of salivary gland stones: first clinical experiences. J Stone Dis 1992; 4: 8-12.
17. Sackmann M, Delius M, Sauerbruch T et al. Shock-wave lithotripsy of gallbladder stones. The first 175 patients. N Engl J Med 1988; 318: 393-7.
18. Ell C, Kerzel W, Heyder N, Becker V, Hermanek P, Domschke W. Piezo-electric lithotripsy of gallstones. Lancet 1987; ii: 1149-50.
19. Norrby S, Schönebeck J. Long-term results with cholecystolithotomy. Acta Chir Scand 1970; 136: 711-3.
20. Zeman RK, Al-Kawas F, Benjamin SB. Gallstone lithotripsy: is there still cause for optimism? Radiology 1991; 178: 33-5.
21 Iro H, Nitsche N, Schneider HT, Ell C. Extracorporeal shockwave lithotripsy of salivary gland stones. Lancet 1989; ii: 115.
22. Russo P, Stephenson RA, Mies C et al. High energy shock waves suppress tumor growth in vitro and in vivo. J Urol 1986; 135: 626-8.

23. Russo P, Mies C, Huryk R, Heston WDW, Fair WR. Histopathologic and ultrastructural correlates of tumor growth suppression by high energy shock waves. J Urol 1987; 137: 338-41.

24. Goetz AE, Königsberger R, Gamarra F et al. Shockwave induced collapse of the tumor microcirculation: intravital microscopy (IM) and magnetic resonance imaging (MRI). Eur Surg Res 1988; 20(suppl 1): 118.

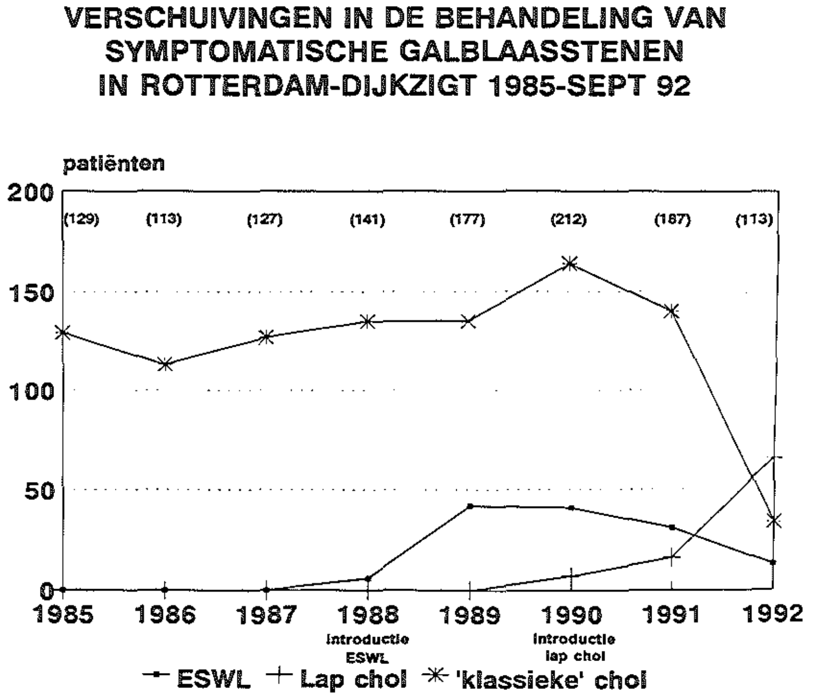
25. Dongen van JW, Steenbrugge GJ van, Romijn JC, Schröder FH. The cytocidal effect of high energy shock waves on human prostatic tumour cell lines. Eur J Cancer Clin Oncol 1989; 25: 1173-9.

26. Kaulesar Sukul DMKS, Johannes EJ, Pierik EGJM, Eijck van GJWM, Kristelijn MJE. The effect of high energy shock waves focussed on cortical bone; an in vitro study. J Surg Res; in press.

27. Johannes EJ, Kaulesar Sukul DMKS, Pierik EGJM, Kristelijn MJE, Eijck van GJWM, Bras J. Non-operative treatment of nonunions in bone with extracorporeal shock waves. Eur Surg Res 1992; 105: 24.

SAMENVATTING

Cholecystectomie is een effectieve behandeling voor symptomatische galblaasstenen, echter de morbiditeit (10%), de mortaliteit (0,3%) en de met de operatie gepaard gaande kosten hebben de research naar niet-operatieve behandelwijzen gestimuleerd. Nadat in 1972 aangetoond was dat galstenen opgelost konden worden door middel van oraal toegediende galzuren was de cholecystectomie niet langer de enige therapeutische optie voor de behandeling van galstenen. Hierna werden verschillende alternatieve therapieën voor de cholecystectomie ontwikkeld. De onderzoeken beschreven in dit proefschrift zijn alle op het gebied van de niet-operatieve behandeling van gal- en pancreasstenen.



Figuur 1. Verschuivingen in de behandeling van symptomatische galblaasstenen in het Academisch Ziekenhuis Rotterdam 'Dijkzigt' (1985-1992). Totaal aantal patiënten behandeld voor symptomatische galblaasstenen tussen haakjes.

ESWL=extracorporele schokgolf vergruizing; lap chol=laparoscopische cholecystectomie; 'klassieke' chol=acute en electieve klassieke cholecystectomieën.

De klinische introductie van extracorporele schokgolf vergruizing (ESWL) in 1980 veranderde de behandeling van nierstenen drastisch. Operatieve therapie voor nierstenen, hetgeen tot die tijd de enige therapie was, wordt nu nog slechts uitgevoerd bij 5% van alle patiënten.

Sinds deze fascinerende resultaten zijn gepubliceerd, is veel wetenschappelijk onderzoek verricht om de klinische toepasbaarheid van schokgolven te verruimen. Nadat de effectiviteit en de veiligheid van ESWL bij proefdieren was onderzocht, werd ESWL klinisch toegepast bij de behandeling van stenen in de galblaas, de intra- en extrahepatische galwegen, de ductus pancreaticus en de speekselklieren.

Met name de introductie van ESWL in 1985 en de laparoscopische cholecystectomie in 1987 hebben een enorme invloed gehad op het beleid bij de behandeling van cholecystolithiasis. In Figuur 1 staan de verschuivingen in de verschillende therapeutische opties voor galblaasstenen in de laatste 7 jaar in het Academisch Ziekenhuis 'Dijkzigt'-Rotterdam (introductie ESWL 1988, introductie laparoscopische cholecystectomie 1990). Het aantal "klassieke" cholecystectomieën steeg gering in 1990. Deze stijging werd waarschijnlijk veroorzaakt door het openen van een speciale polikliniek (in het AZR-'Dijkzigt') voor patiënten met galblaasstenen in 1989. Hierdoor nam het totaal aantal verwezen patiënten met galblaasstenen naar ons ziekenhuis toe. De figuur laat tevens zien dat het aantal "klassieke" cholecystectomieën en het aantal ESWL-behandelingen in 1992 afnam. Vanaf dit jaar werd de laparoscopische cholecystectomie de therapie van keuze in het AZR-'Dijkzigt'.

Hoofdstuk 1 geeft een algemeen overzicht van de geschiedenis, de epidemiologie en de verschillende behandelingen voor galstenen. Tevens worden in dit hoofdstuk de vraagstellingen geformuleerd.

Hoofdstuk 2 beschrijft de Rotterdamse ervaring met ESWL voor galblaasstenen. ESWL voor galblaasstenen heeft niet kunnen voldoen aan de hooggespannen verwachtingen, die gewekt werden na de eerste veelbelovende publicaties. Onze conclusie is dat ESWL voor symptomatische galblaasstenen, gecombineerd met adjuvante therapie met orale galzuren, veilig en relatief effectief is voor een zeer geselecteerde groep van patiënten. Deze behandeling dient gereserveerd te worden voor patiënten met een verhoogd operatie-risico of voor patiënten die geen chirurgische therapie wensen.

Hoofdstuk 3 heeft betrekking op de noodzaak van een adjuvante behandeling na ESWL teneinde de resterende steenfragmenten op te lossen of zodanig te verkleinen dat deze met de faeces het lichaam kunnen verlaten. Meestal geschiedt deze nabehandeling door middel van oraal toegediende galzuren. Dit is echter een langdurige en kostbare behandeling. In dit hoofdstuk worden de resultaten besproken van simultane behandeling van galstenen met ESWL en methyl *tert*-butyl ether (MTBE) in vitro en in een proefdiermodel. De effectiviteit van deze combinatietherapie in vitro was veelbelovend, echter in het proefdiermodel lukte het niet om de steen met echografie goed te visualiseren. Derhalve waren de resultaten in vivo teleurstellend. Wel kon aangetoond worden dat de combinatietherapie geen extra weefselschade veroorzaakte. Meer onderzoek is nodig om de visualisatie te verbeteren voor deze (in vitro) veelbelovende niet-operatieve behandeling van galblaasstenen.

Hoofdstuk 4 benadrukt het belang van de echografie in het evalueren van de resultaten van ESWL voor galblaasstenen. De echografische bevindingen na ESWL werden geanalyseerd en gerelateerd aan de resultaten van ESWL. Hiertoe werden opeenvolgende echografische onderzoeken na ESWL met elkaar vergeleken. Uit deze studie bleek dat echografie beperkingen had in de evaluatie van het resultaat van een ESWL behandeling. Echografie beïnvloedde het klinische beloop op twee manieren: overschatting van de effectiviteit door ten onrechte geen stenen of fragmenten in de galblaas aan te tonen en onderschatting van de fragmentgrootte na ESWL. Dit resulteerde in een onjuist uitstel van herbehandeling van de patiënt. Om dit te voorkomen wordt geadviseerd een tweede (verificatie) echografie te vervaardigen, wanneer echografisch geen fragmenten worden aangetoond of wanneer fragmenten kleiner dan 5 mm worden gezien, voordat besloten wordt de ESWL behandeling te staken.

In *Hoofdstuk 5* wordt ingegaan op 7 verschillende behandelmodaliteiten van galblaasstenen en welke patiënten hiervoor in aanmerking komen (inclusie-percentage), gebaseerd op een analyse van bijna 700 patiënten die de galsteenpolikliniek van het Academisch Ziekenhuis Rotterdam-Dijkzigt bezochten. Deze 7 therapieën zijn: "klassieke cholecystectomie", laparoscopische cholecystectomie, oraal toegediende galzuren, locale oplostherapie met MTBE, ESWL, percutane cholecystolithotomie, en 'rotary' contact lithotripsie. De inclusie-percentages waren het hoogst voor operatieve behandeling (86-97%) en het laagst voor ESWL (18%). Wanneer gekeken wordt naar deze inclusie-percentages, de succes percentages, het aantal complicaties en de kans op terugkeer van stenen is het onze mening dat op dit moment laparoscopische cholecystectomie de beste behandeling is voor patiënten met symptomatische galblaasstenen zonder verhoogd operatie-risico. Wel denken wij dat er een plaats zal blijven bestaan voor de niet-operatieve behandelingen van galstenen, speciaal voor patiënten met een verhoogd operatie-risico of voor patiënten die operatieve therapie afwijzen.

Hoofdstuk 6 behandelt het nadeel van alle galblaas preserverende therapieën, namelijk de kans op de nieuwe vorming van stenen. Na een literatuurstudie bleek dat terugkeer van stenen onvermijdelijk is bij de meeste patiënten wanneer de nabehandeling gestopt wordt na succesvolle galblaassparende therapie. Sommige onderzoekers rapporteren dat circa 80% van de patiënten opnieuw stenen krijgen. Tot nu toe heeft medicamenteuze preventie van de nieuwe vorming van stenen nog niet tot een bevredigend resultaat geleid. Echter het onderzoek staat in de meeste gevallen nog in de kinderschoenen. Occlusie van de ductus cysticus en chemisch scleroseren van de galblaas is een recente ontwikkeling in de preventie-onderzoeken. De eerste resultaten van deze invasieve methode lijken veelbelovend. Wel dient de techniek nog verbeterd te worden wil deze methode een serieus alternatief voor chirurgische cholecystectomie worden.

Hoofdstuk 7 geeft de resultaten van ESWL voor stenen in de galwegen. Tot voor kort was chirurgische exploratie voor stenen in de ductus choledochus een geaccepteerde therapie. Deze operatie kent echter een aanzienlijke morbiditeit en mortaliteit, vooral in de oudere patiëntenpopulatie. Na de introductie van de endoscopische steenextractie na papillotomie (dit is mogelijk in 90% van de patiënten) werd dit al snel de therapie van keuze voor galwegstenen wanneer er geen stenen in de galblaas aanwezig zijn of wanneer de patiënt een cholecystectomie ondergaan heeft. ESWL voor stenen in de galwegen is een effectieve en veilige behandeling van galwegstenen. Deze behandeling moet overwogen worden vóór chirurgisch ingrijpen wanneer endoscopische steenextractie niet mogelijk is. Meestal was het nodig om na de ESWL nog een aanvullende behandeling te geven in de vorm van spoelen van de galwegen of endoscopische en/of percutane transhepatische procedures om de galwegen geheel vrij van steen(fragmenten) te krijgen.

Hoofdstuk 8 beschrijft de resultaten van ESWL voor stenen in het pancreas. Chronische calcificerende pancreatitis (meestal veroorzaakt door een overmatig alcoholgebruik) is een groot klinisch probleem. Endoscopische en chirurgische behandeling hebben lage succes-percentages, een hoge morbiditeit en een niet te verwaarlozen mortaliteit. Wij hebben de toepasbaarheid van ESWL voor de behandeling van pancreasstenen onderzocht en kwamen tot de conclusie dat dit een veilige therapie is met bevredigende resultaten. Opvallend was dat sommige patiënten verlichting van de klachten hadden zonder dat de ductus pancreaticus totaal vrij van stenen werd. Onze nacontrole is echter nog te kort en het aantal patiënten te klein om definitieve conclusies te kunnen trekken.

Epiloog

Wanneer we alle resultaten bekijken is het onze mening dat er een plaats zal blijven voor ESWL voor de behandeling van galstenen. De laparoscopische cholecystectomie is de therapie van keuze voor patiënten met symptomatische galblaasstenen. ESWL dient gereserveerd te worden voor patiënten met een verhoogd operatie-risico of voor patiënten die operatieve behandeling afwijzen. ESWL voor stenen in de galwegen en in het pancreas is de eerste therapeutische optie voor de oudere patiënt bij wie endoscopische steenextractie gefaald heeft.

ESWL voor gal- en pancreasstenen dient geconcentreerd te worden in centra waar ook ESWL voor nierstenen plaatsvindt. Enerzijds zullen op deze wijze centra ontstaan met een ruime ervaring met schokgolf therapieën, anderzijds kunnen de kosten van de vergruizingsapparatuur worden gerechtvaardigd door een effectiever gebruik van de apparatuur.

Tenslotte een paar woorden over de toekomstige toepasbaarheid van ESWL in de geneeskunde, anders dan bij de behandeling van nier- en galstenen. Recent zijn de eerste hoopvolle resultaten gepubliceerd van ESWL voor stenen in de speekselklieren. ESWL voor de behandeling van maligniteiten bevindt zich nog steeds in de experimentele fase. Daarom kan over deze toepassing nog geen duidelijke standpunt worden ingenomen. De laatste ontwikkeling op ESWL-gebied is die voor de behandeling van hypertrofische pseudoarthrose. ESWL "lijkt" een goed alternatief voor chirurgische interventies bij deze afwijking.

Ondanks het feit dat nog niet kan worden overzien wat de uiteindelijke rol van ESWL in de behandeling van patiënten met een chirurgisch te cureren aandoening zal zijn, is ESWL inmiddels uitgegroeid tot een chirurgisch wapen net als het scalpel en de laserstraal.

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CURRICULUM VITAE

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