ASPECTS OF THE CURRENT TREATMENT MODALITIES FOR SYMPTOMATIC GALLSTONES

ASPECTS OF THE CURRENT TREATMENT MODALITIES FOR SYMPTOMATIC GALLSTONES

ASPECTEN VAN DE HUIDIGE BEHANDELMETHODEN VOOR SYMPTOMATISCHE GALSTENEN

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr P.W.C. Akkermans M. Lit.
en volgens besluit van het College der Dekanen.
De openbare verdediging zal plaatsvinden op
woensdag 30 maart 1994 om 11.45 uur.

door

Peter William Plaisier

geboren te Rotterdam

Promotiecommissie

Promotores:	Prof. Dr H.A. Bruining
	Prof. Dr O.T. Terpstra
Overige leden:	Dr J.S. Laméris
	Prof. Dr S.W. Schalm

1994
PASMANS OFFSETDRUKKERIJ B.V., DEN HAAG

aan: mijn ouders
Ieneke

CONTENTS

Background and aims of the study

Background

Extracorporeal shock wave lithotripsy (ESWL) of gallbladder stones was clinically introduced in 1985 [1]. Before that, cholecystectomy had been the unchallenged standard therapy for symptomatic gallbladder stones for over a century [2].

Expectations with regard to ESWL ran rather high after publication of the first results in a large series of patients [3]. This actuarial analysis of 175 patients indicated that not less than 91% of the patients rendered stone free at a negligible complication rate. Lay press interpreted these data as if surgery would soon become obsolete for the majority of gallstone patients, an interpretation also heard from optimistic physicians at scientific meetings. As a consequence of this optimism, an unbridled purchase of gallstone lithotriptors occured by hospitals all over Germany, the country of origin of ESWL. This optimism seemed justified because a decade earlier, ESWL revolutionized urological practice. Shortly after the introduction of ESWL, surgery for urinary tract stones became restricted to less than 5% of the patients [4].

The professional attitude in The Netherlands, however, was reserved. Valid studies on the efficacy, safety and cost-effectiveness were requested before ESWL were to be accepted as a serious treatment modality for symptomatic gallstones [5,6]. This inspired our group to start with in vitro and in vivo studies. The whole project was named the Rotterdam Gallstone Study, or ROGAL Study. This ROGAL Study also included a randomized clinical trial and a cost-effectiveness analysis.

Major considerations to perform a prospective randomized study were twofold. First, such a trial was considered essential, because all the then available reports on gallstone lithotripsy were not controlled [7]. And second, because ESWL of urological stones had replaced surgery almost completely despite that a randomized trial was never performed. This had always been a major point of criticism [8].

A cost-effectiveness analysis was initiated for two reasons. First, because of the apparent medical and economical impact of gallbladder stones disease: 10% of the adult population have gallstones [9,10] and approximately 14,000 cholecystectomies are performed in The

Netherlands each year [11]. This accounts for *f*80 million of yearly expenses [11] and an economic evaluation of the consequences of ESWL was, obviously, mandatory. Second, because of the fact that reports on whether ESWL would lead to reduced costs were speculative and contradictory [12,13]. Moreover, the results of a cost-effectiveness analysis would provide information on the general need for lithotriptors in The Netherlands.

The experimental and first clinical results of the ROGAL Study have already been published [14,15]. The results of the randomized study are presented in this thesis.

Aims of the study

Aims of this study were to investigate the particular role of ESWL in the whole spectrum of treatment modalities for symptomatic gallstones. ESWL's potential value was investigated in separate studies. These studies evaluated ESWL in terms of eligibilty, stone clearance, safety, symptom relief, general well being and cost-effectiveness.

During the performance of the ROGAL Study, it became evident that the public's interest in the randomized part of the study was relatively poor. Because this hampered patient accrual, the factors influencing this phenomenon were investigated. One of the major determinants of the loss of interest in ESWL was the introduction of laparoscopic cholecystectomy [16]. This new technique was also evaluated by means of the same questionnaires as used for the evaluation of ESWL. Finally, the potential value of extracorporeal shock waves in fields other than gallbladder stones was studied.

The following questions were discussed in this thesis:

- what are the currently available treatment modalities for symptomatic gallstones? (Chapter 2)
- how many patients are eligible for ESWL? (Chapter 3)
- what is the efficacy and safety of ESWL in a large group of patients? (Chapter 4)
- what is the course of biliary and gastrointestinal symptoms after ESWL in comparison with conventional cholecystectomy, the gold standard? (Chapter 5)

- how is the quality of life after ESWL in comparison with conventional cholecystectomy? (Chapter 6)
- what is the cost-effectiveness of ESWL? (Chapter 7)
- what implications have the findings at oral cholecystography for nonsurgical treatment modalities for symptomatic gallstones? (Chapter 8)
- what factors resulted in a relatively poor patient accrual into the randomized part of the study 'ESWL versus cholecystectomy'? (Chapter 9)
- what is the course of biliary and gastrointestinal symptoms and qualtity of life after laparoscopic cholecystectomy in comparison with conventional cholecystectomy? (Chapter 10)
- what are the potential applications of extracorporeal shock waves in surgery? (Chapter 11)

The ROGAL Study

The clinical study investigating extracorporeal shock wave lithotripsy versus cholecystectomy was subsidized by the Ministry of Education of the Dutch Government as a medical development project. The study was performed at the Department of Surgery of the University Hospital 'Dijkzigt', Rotterdam, The Netherlands. Radiologic screening and follow-up of patients were performed at the Department of Radiology of the University Hospital 'Dijkzigt'. The study protocol was developed with assistance of the Department of Clinical Decision Making of the Erasmus University Rotterdam, Rotterdam, The Netherlands. The cost-effectiveness analysis was performed in close cooperation with the Institute for Medical Technology Assessment of the Erasmus University Rotterdam. The study protocol was approved by the Medical Ethics Committee of the University Hospital 'Dijkzigt' and the Erasmus University Rotterdam.

References

1. Sauerbruch T, Delius M, Paumgartner G, et al. Fragmentation of gallstones by extracorporeal shock waves. N Eng J Med 1986;314:818-22.
2. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989;158:174-8.
3. 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.
4. Chaussy CG, 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.

5. Vergunst H, Terpstra OT, Brakel K, et al. Extracorporele schokgolf-lithotripsie (ESWL) als niet-invasieve behandelingsmethode van galstenen. Ned Tijdschr Geneeskd 1988;132:1965-70.
6. Erpecum van KJ, Stolk MFJ, Berge Henegouwen van GP, et al. Schokgolflithotripsie van galstenen. Ned Tijdschr Geneesk 1990; 134:112-5.
7. Nijs HGT, Toom R den, Berger M, et al. Extracorporeal shock wave lithotripsy versus cholecystectomy: the need for randomized clinical trials. J Lithotrispy Stone Dis 1991;3:112-3.
8. Dudley HAF. Stones, lithotriptors, trials and arguments. BMJ 1986;292:846-7.
9. Pixley F. Epidemiology. In: Bateson MC (ed). Gallstone disease and its management. Lancaster, PA:MTP Press, 1986.
10. Jörgenson T. Prevalence of gallstones in a Danish population. Am J Epidemiol 1987;126:12-21.
11. Stichting Medische Registratie, Utrecht 1987.
12. Nealon WH, Urrutia F, Fleming D, et al. The economic burden of gallstone lithotripsy: will cost determine its fate? Ann Surg 1991;213:645-50.
13. Stengele U, Baumgartner BR, Chezmar JL, et al. Biliary lithotripsy versus cholecystectomy: a cost utility analysis. J Lithotripsy Stone Dis 1991;3:133-40.
14. Vergunst H. Extracorporeal shockwave lithotripsy of galbladder stones: an experimental study [thesis EUR, 1991]. ISBN 90-9004573-2.
15. Toom R den. Extracorporeal shock wave lithotripsy of biliary and pancreatic stones [thesis EUR, 1993]. ISBN 90-9006102-9.
16. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991;324:1073-8.

CHAPTER 2

The current treatment modalities for symptomatic gallstones

P.W. Plaisier, R.L. van der Hul, O.T. Terpstra, H.A. Bruining

Am J Gastroenterol 1993;88:633-9

Abstract

Gallstone disease is an important clinical problem: approximately 10% of all adults in the western population have gallstones. Most gallstones, however, remain asymptomatic and from various disciplines there is consensus that only symptomatic gallstones require therapy. Since the first gallbladder extirpation in 1882, cholecystectomy has been considered the gold standard. Nowadays, this operation is performed laparoscopically in most hospitals. Despite relatively low morbidity and mortality rates, a number of alternative therapies have been developed in the past few years. These alternative treatment modalities are especially indicated in high risk patients and in patients rejecting surgery. In this review article the currently available treatment modalities are discussed.

Introduction

Gallstone disease is an important clinical problem with tremendous economic consequences. About 10% of the adult population have gallstones [1,2] and approximately 500,000 cholecystectomies are performed annually in the United States [3]. As a consequence, more than three million hospital days and one billion dollars are spent on cholecystectomy every year [4]. Gallstones cause symptoms in the minority of patients: it is estimated that only 10-15% of the patients ever become symptomatic [5]. This understanding led to consensus that only symptomatic gallstones require therapy [6-8].

Since the first succesful gallbladder extirpation in 1882, cholecystectomy has been considered the therapy of choice for symptomatic gallstones [9]. Although cholecystectomy has become a routine operation in experienced hands, it is still accompanied by considerable morbidity and mortality. This fact led to extensive research for alternative, preferably noninvasive, treatment modalities for gallstone disease.

The different treatment modalities for symptomatic gallstones are discussed in this review. The major exclusion criteria for the different treatment modalities are depicted in Table 1.

1. Open cholecystectomy

In 1882 the first gallbladder extirpation was performed in Germany [10]. Cholecystectomy is considered curative but is accompanied by a morbidity of 10-30% and a mortality of 0.1-0.6% [9,11,12]. Both percentages increase with age, concomitant disease or when the procedure is accompanied by common bile duct exploration [11]. Access to the gallbladder can be achieved via three different incisions (subcostal, abdominal transverse and midline). Reports on which incision is preferable are controversial in terms of postoperative complications [13,14]. Therefore, it is in fact the surgeon's preference that determines the sort of incision. The most serious complication of cholecystectomy is an accidental bile duct lesion, which usually leads to serious morbidity and even mortality [15,16]. Bile duct lesions occur in 1-2 per 1000 operations [15] and are related to the surgeon's skill, variations in anatomy and inflammatory local conditions [16]. Most bile duct injuries are discovered in the postoperative phase [17] and only approximately 20% are discovered intraoperatively. This rate increases if a cholangiogram is performed routinely [15,16]. Although the incidence of bile duct injuries is related to the surgeon's skill, injuries are not caused by lack of

experience. Surprisingly, it was found that most accidental lesions are caused by surgeons and surgical trainees, who had performed more than 25 but less than 100 cholecystectomies [15]. Hospitalization time for a classic cholecystectomy averages about a week and has decreased gradually in the last few years [12]. Even, discharge within 24 h after elective cholecystectomy has been described [18]. Except for high anesthesia risk, there are in fact no contraindications for classic cholecystectomy (Table 1).

2. Bile acid therapy

The first attempts to dissolve gallstones by oral medication go back as far as 1937 [19], although the concept of dissolving gallstones had already been discussed in 1873 [20]. Almost 100 yr later, clinical administration of bile acids appeared to be feasible [21,22]. Chenodeoxycholic acid (chenodiol or CDC) and its 7ß-epimer ursodeoxycholic acid (ursodiol or UDC), have been successful in dissolving gallstones [21-24]. Both bile acids occur naturally in humans and several other species.

The exact biochemical mechanism by which cholelitholysis is achieved, is complex [25]. In fact, two main activities are involved: bile desaturation and actual dissolution. The mechanism by which UDC and CDC reduce cholesterol saturation and dissolve cholesterol gallstones involves enrichment of the bile acid pool with the administered bile acids. Furthermore, hepatic cholesterol secretion into bile is inhibited by CDC, because it interferes with the cholesterol-synthezing enzyme HMG-CoA-reductase [26-28]. Actual dissolution is achieved by transfer of cholesterol into micelles and vesicles. Transfer into micelles is enhanced by both CDC and UDC, whereas transfer into vesicles occurs mainly by UDC [25]. Finally, UDC is believed to reduce intestinal uptake of cholesterol [28], although evidence in this regard is conflicting [29].

CDC therapy is associated with several dose-related side effects, such as diarrhea and clinically nonsignificant increases in transaminases and serum cholesterol [25,30-33]. UDC is not associated with toxic side effects [34], but is more expensive than CDC. For this reason, and because side effects of CDC are milder if low-dosage CDC therapy is combined with UDC, in Europe a combination therapy is to be preferred to CDC alone [35]. It is not clear whether combination therapy is more effective than UDC alone [36,37].

Advised doses are 15 mg CDC/kg/day and 8-13 mg UDC/kg/day, respectively, or 7.5 mg CDC/kg/day and 6.5 mg UDC/kg/day, if UDC and CDC are combined [25,34,35,38].

Evidence as to whether absorption of UDC is better as a bedtime dose than as a mealtime dose is conflicting [39,40]. For CDC and the combination of UDC and CDC, a bedtime dose is advised [26,40-42].

UDC seems to be more resistant to bacterial destruction than CDC, which explains why UDC is effective at a smaller dose than CDC [43]. It also explains why UDC is less toxic: due to less bacterial destruction, less toxic side products, such as lithocholic acid, are formed [44].

Oral bile acid [OBA] therapy is rather time consuming. Usually, treatment must be continued for at least some months and frequently for several years [45]: the rate of decrease of gallstone diameter appears to be approximately 1 mm per month [46]. Therefore, stone diameter is a major determinant of effectiveness of oral dissolution [46]. If the stones are smaller than 1 cm in diameter, few in number, the cystic duct is patent and the patient is compliant with the treatment, the likelihood of success is about 60% [33,47]. This success rate decreases when stones are larger or multiple [42,47]. Stones larger than 1cm are therefore considered a relative contraindication for OBA therapy [48] and stones larger than 15-20 mm unsuitable for oral dissolution alone [38,47,48].

Pregnancy or a planned pregnancy is a contraindication for CDC therapy, which is thought to cross the placenta, possibly damaging the fetal liver [49]. Opinions on a possible teratogenicity of UDC are conflicting [26,50-52], but recently pregnant women with intrahepatic cholestasis were treated with UDC successfully, without any adverse effect for their babies [53]. In conclusion, OBA therapy can be effective, but only in selected patients (Table 1). Stone recurrence is a serious problem (discussion).

3. Contact dissolution

Local contact dissolution of gallbladder stones is much less time consuming than oral litholysis, but is invasive. Nevertheless, it can be performed without general anesthesia [54], thus being applicable to high-surgical-risk patients. The solvent most applied, is methyl-tert-butyl-ether (MTBE) [54,55], which is also capable of dissolving stones in the common bile duct. Several other agents, such as monooctanoin [56], limonene [57] and ethyl propionate [58], have also proved to be effective. EDTA has not been tested in vivo, but in vitro studies show that EDTA is capable of dissolving cholesterol stones with minor calcifications [59].

Dissolving agents can be infused via a catheter, which can be installed into the

gallbladder either transhepatically [60] or endoscopically [61]. Dissolution can be accomplished after repeated cycles of infusion and complete aspiration of the dissolving agent [47,53]. Although infusion may take even more than 1 day, median treatment times with MTBE are approximately 6 h for solitary stones and 7 h for multiple stones [62]. A pump system for automatic delivery of the solvent was recently introduced [63].

In vitro comparison of the dissolving capacity of MTBE, monooctanoin, limonene and a limonene/monooctanoin mixture showed that MTBE is the most potent gallstone solvent now available [64]. In vivo MTBE dissolves gallbladder stones 50 times faster than monooctanoin [60].

MTBE dissolution therapy is inexpensive [65-67] and very effective: reports show dissolution rates as high as 95% [54,68]. Slightly echogenic debris remains in most of the cases [54]. Side effects include hemolysis and duodenitis in case of overflow and, due to systemic absorption, nausea and somnolence. When absorbed, MTBE is eliminated almost intact by exhalation [69]. Like oral bile acids, MTBE has been used as adjuvant therapy after extracorporeal shock wave lithotripsy (ESWL) [70], but up to now it has not been used routinely for this purpose.

Because of its invasive character and potentially serious side effects, contact dissolution should be confined to specialized centers [71].

4. Extracorporeal shock wave lithotripsy

In 1980 the first clinical experience with ESWL for the treatment of kidney stones was reported [72]. ESWL has now become the therapy of choice in the case of urolithiasis. Surgical treatment is restricted to less than 5% of patients [73]. Because of the good results in urology, other applications of ESWL have been studied. ESWL for gallbladder stones has been applied since 1985 [74,75].

Shockwaves are characterized by ultrashort, high-pressure amplitudes and they obey the physical laws of acoustics. The shockwaves are focused on the stone and they travel through the body without causing severe tissue damage because water, the transmission medium, absorbs very little acoustic energy and the acoustical impedance of soft body tissues is close to that of water. The shockwave energy is released at the interface of body tissues and the stone surface because of the abrupt change of acoustic impedance. This causes tear-and-shear forces, which together with the formation of cavitation bubbles on the surface of the stone,

lead to progressive stone disintegration [76,77].

Shockwaves can be generated by three methods: by an underwater electrostatic spark-gap discharge, by electromagnetic generation or by piezo-electric generation [78]. Spontaneous passage of fragments up to 5 mm through the cystic duct and the papilla of Vater without clinical or biochemical symptoms has been observed [79]. Fragments larger than 5 mm are less likely to be cleared spontaneously and this underlines the necessity for adjuvant dissolution therapy of fragments [31]. ESWL can be performed under intravenous analgo-sedation on an outpatient basis [80,81]. The treatment time averages 1 h (range: 26-210 min) and usually 1-2 sessions are required [31,75,80-83].

ESWL is limited by restricted eligibility, moderate results and the possibility of stone recurrence. Suitability for ESWL depends on a large number of conditions, which are depicted in Table 1. It should be noted, however, that these exclusion criteria are the initial criteria of the Munich group [75], and have been widened by other authors [81,84,85], as well as by the Munich group itself [80,86]. Due to the rigid entry criteria, only 10-53% of the patients are eligible for ESWL [75,80,87-92]. Overall stone free rates at 12 months vary between 30 and 78% [75,80,83,84,93], but therapy is found to be more effective for solitary than multiple stones, for radiolucent than slightly calcified stones, and for smaller than for larger stones [31]. Reliable long-term data on stone recurrence rates after succesful ESWL are still not available [80], but medium-term results suggest a recurrence rate of 20% in 4 yr [94], which is in fact lower than in other alternative, gallbladder preserving, therapies [80,81]. Despite these limitations of ESWL and the necessity of adjuvant therapy, morbidity and mortality are minimal [75,80,81,84]. ESWL of gallstones is therefore especially indicated for patients with a high surgical risk.

5. Cholecystolithotomy

Endoscopic removal or lithotripsy of gallbladder stones via a percutaneous transperitoneal approach offers the advantage of immediate removal of all stone material regardless of number, composition or size (Table 1). With sterile techniques, the gallbladder fundus is located and punctured under radiologic guidance and analgo-sedation. For about 2 wk, a catheter must be left behind for drainage. Percutaneous techniques are technically demanding [95] and are therefore performed in a few specialized centers only.

Success rates of cholecystolithotomy are reportedly up to 95%, although often more than

one stone removal session is necessary [95-101]. Nonfatal complications occur in about 13% of the patients [101].

6. Rotary contact lithotripsy

Rotary contact lithotripsy involves the placement of a special instrument. This device includes an impeller that rotates up to 30,000 rpm and a six-pronged metal basket for protection of the gallbladder wall. While the rotating impeller creates a powerful vortex, that automatically pulls the calculi into the basket, fragmentation to concrements <0.5 mm is easily achieved [102]. The procedure takes about 10-60 min, depending on the stone load and stone composition [103]. Because of its recent introduction, little information is available on morbidity, apart from the encountered drain-related problems. No mortality has been reported.

7. Laparoscopic cholecystectomy

The first series of laparoscopic cholecystectomies was reported in France in 1987 [104]. Under general anesthesia, a pneumoperitoneum is created by insufflation with carbon dioxide. Via four abdominal incisions with a diameter of less than 1 cm each, surgical instrumentation is introduced. In fact the laparoscopic cholecystectomy is a variant of the open cholecystectomy. Here, also, the gallbladder is removed after ligation of the cystic duct and artery.

Major advantages of this technique are a markedly diminished need for postoperative narcotic analgetics, early discharge from the hospital and a quicker return to work [105-107]. The cosmetic result (the absence of a large scar), is experienced a major advantage. Absolute contraindications are sepsis, peritonitis and distended bowels [108]. Relative contraindications are previous upper abdominal surgery and an inflamed gallbladder; the two main causes of conversion to open cholecystectomy in about 5-10% of the cases [105,109,110].

The most serious complication of the laparoscopic cholecystectomy is bile duct injury. For the most part, this is the result of misidentification of the common bile duct for the cystic duct or inaccurate placement of clips. The reported higher incidence of this complication in laparoscopic than in open cholecystectomy gives reason for some concern [105,111,112]. The incidence of common bile duct lesions is expected to decrease after the initial learning curve. Other complications are comparable to the open technique, but may cause conversion to an

open cholecystectomy, e.g. in case of a laparoscopically uncontrollable arterial bleeding. The number of contraindications is thought to decrease as the result of growing experience with the technique: already-pregnant women have been treated successfully with laparoscopic cholecystectomy in the first and second trimester [113].

When common bile duct stones are suspected, an intraoperative cholangiography can be performed easily [114-116]. When found, one could consider converting to open cholecystectomy with common bile duct exploration or performing endoscopic retrograde cholangio-pancreatography [ERCP] afterwards. In cases in which common bile duct stones are demonstrated in the preoperative work-up, extraction by ERCP can be achieved prior to laparoscopic cholecystectomy. Even common bile duct surgery via the laparoscope appears feasible [116,117]. Although in most cases laparoscopic cholecystectomy is performed under general anesthesia [105,109,110], it is also done under epidural anesthesia [118]. Although hospitalization is still the rule, laparoscopic cholecystectomy can be performed on an outpatient basis [118,119].

Discussion

Gallstones are of great clinical importance for which different treatment modalities are available nowadays. Other methods, such as laser lithotripsy, are still experimental [120,121].

For more than a century, operative extirpation of the gallbladder has been the therapy of choice in case of symptomatic cholelithiasis for two basic reasons. First, cholecystectomy is applicable in almost any patient, and second, there is no possibility of stone recurrence. Laparoscopic cholecystectomy seems to (re-)confirm this view and, moreover, it has apparent advantages over the open technique. Still, critical evaluation of morbidity and mortality of this technique are necessary and data on the incidence of bile duct lesions are especially important [105,111,112].

Alternative methods are less invasive, but both eligibility and results are often limited. Besides the necessity for a more extended diagnostic work-up, the largest problem of alternative gallstone treatment seems to be stone recurrence, which is estimated to be about 10%/yr with a stabilization after 5 years [122-126]. However, recurrence is more frequent after treatment of multiple stones than of solitary stones [126].

It is expected that the laparoscopic cholecystectomy will be the new gold standard [127].

Alternative treatment modalities will then be reserved especially for those patients with a high surgical risk and for those patients, who are unwilling to be operated.

References

1. Pixley F. Epidemiology. In: Bateson MC (ed). Gallstone disease and its management. Lancaster, PA:MTP Press, 1986.
2. Jörgenson T. Prevalence of gallstones in a Danish population. Am J Epidemiol 1987;126:12-21.
3. Simeone JT, Ferruci JT. New trends in gallstone imaging. JAMA 1981;246:380-3.
4. Sonnenberg E van, Hofmann AF. Horizons in gallstone therapy. Am J Roentgenol 1988;150:43-6.
5. Thistle JL, Cleary PA, Lachin JM. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med 1984;101:171-5.
6. Finlayson N. Cholecystectomy for gallstones. A good thing if they cause symptoms. Br Med J 1989;298:133-4.
7. Ransohoff DF, Gracie WA, Wolfensom LW. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 1983;99:199-204.
8. 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.
9. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989;158:174-8.
10. Langenbuch C. Ein Fall von Extirpation der Gallenblase wegen chronischer Cholelithiasis. Heilung. Berliner Klin Wochenschr 1882;19:725-7.
11. McSherry CK, Glenn F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. Ann Surg 1980;191:271-5.
12. Gutman H, Kott I, Haddad M, et al. Changing trends in surgery for benign gallbladder disease. Am J Gastroenterol 1988;83:545-8.
13. Garcia-Valdecasas JC, Almenara R, Cabrer C, et al. Subcostal incision versus midline laparotomy in gallstone surgery: a prospective and randomized trial. Br J Surg 1988;75:473-5.
14. Cahalane MJ, Shapiro ME, Silen W. Abdominal incision: decision or indecision? Lancet 1989;i:146-8.
15. Andrén-Sandberg A, Alinder G, Benmark S. Accidental lesions of the common bile duct at cholecystectomy. Pre- and perioperative factors of importance. Ann Surg 1985;201:328-32.
16. Targarona EM, Garcia Olivares E, Marco C. Why and when bile duct injury occurs. HPB Surg 1992;5(suppl):7.
17. Blumgart LH, Kelley CJ, Benjamin IS. Benign bile duct stricture following cholecystectomy: critical factors in management. Br J Surg 1984;71:836-43.
18. Moss G. Discharge within 24 hours of elective cholecystectomy: the first 100 patients. Arch Surg 1986;121:1159-61.
19. Rewbridge AG. The disappearance of gallstone shadows following the prolonged administration of bile acids. Surgery 1937;1:395-400.
20. Schiff M. Il colceinato di soda nella cura dei calcoli biliari. L'Imparziale 1873;13:97-8.
21. Danzinger RG, Hofmann AF, Schoenfield LJ, et al. Dissolution of cholesterol stones by chenodeoxycholic acid. N Engl J Med 1972;286:1-8.
22. Bell GD, Whitney B, Dowling RH. Gallstone dissolution in man using chenodeoxycholic acid. Lancet 1972:ii;1213-6.
23. Bachrach WB, Hoffmann AF. Ursodeoxycholic acid in the treatment of cholesterol cholelithiasis. Dig Dis Sci 1982:27;737-61.
24. Stiehl A, Raedsch R, Czygan P, et al. Effects in biliary cholesterol saturation in gallstone patients treated with chenodeoxycholic acid and/or ursodeoxycholic acid. Gastroenterology 1980;79:1192-98.
25. Sahlin S, Thyberg P, Ahlberg J, et al. Distribution of cholesterol between vesicles and micelles in human gallbladder bile: influence of treatment with chenodeoxycholic acid and ursodeoxycholic acid. Hepatology 1991;13:104-10.
26. Maudgal DP, Northfield TC. A practical guide to the nonsurgical treatment of gallstones. Drugs

1991;41:185-92.
27. Salen G, Nicolau G, Shefer S. Chenodeoxycholic acid inhibits elevated hepatic HMG-CoA-reductase activity in subjects with gallstones. Clin Res 1973;21:523.
28. Coyne MJ, Bonorris GG, Golstein JS, et al. Effect of chenodeoxycholic acid on the rate limiting enzymes of hepatic cholesterol and bile synthesis in patients with gallstones. J Lab Clin Med 1976;87:281-91.
29. LaRusso NF, Thistle JL. Effect of litholytic bile acids on cholesterol absorption in gallstone patients. Gastroenterology 1983;84:265-71.
30. Hofmann AF. Medical dissolution of gallstones by oral bile acid therapy. Am J Surg 1989;158:198-204.
31. Schoenfield LJ, Berci G, Carnovale RL, et al. The effect of ursodiol on the efficacy and safety of extracorporeal shock-wave lithotripsy of gallstones. The Dornier National Biliary Lithotripsy Study. N Engl J Med 1990;323:1239-45.
32. Mok HYI, Bell GD, Dowling RH. The effect of different doses of chenodeoxycholic acid and of withdrawing treatment on bile lipid composition. Lancet 1974;ii:253-7.
33. Roehrkasse R, Fromm AF, Malavolti M, et al. Gallstone dissolution treatment with a combination of chenodeoxycholic and ursodeoxycholic acids. Studies of safety, efficacy and effects on bile lithogenicity, bile acid pool and serum lipids. Dig Dis Sci 1986;31:1032-40.
34. Lanzini A, Northfield TC. Review article: bile acid therapy. Aliment Pharmacol Therap 1990;4:1-24.
35. Roda E, Bazzioli F, Labate AM, et al. Ursodeoxycholic acid vs. chenodeoxycholic acid as cholesterol dissolving agents: a comparative randomized study. Hepatology 1982;2:804-10.
36. Podda M, Zuin M, Battezzati PM, et al. 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.
37. Sackmann M, Pauletzki J, Aydemir U, et al. Efficacy and safety of ursodeoxycholic acid for dissolution of gallstone fragments: comparison with the combination of ursodeoxycholic acid and chenodeoxycholic acid. Hepatology 1991;14:1136-41.
38. Fromm AF, Roat JW, Gonzalez V, et al. Comparative efficacy and side effects of ursodeoxycholic acid and chenodeoxycholic acids in dissolving gallstones: a double-blind controlled study. Gastroenterology 1983;85:1257-64.
39. Walker S, Rudolph G, Raedsch R, et al. Intestinal absorption of ursodeoxycholic acid is dose dependent in patients with extrahepatic biliary obstruction and bile drainage. Gastroenterology 1991;100:A344.
40. Northfield TC, Jazrawi RP, Petroni ML. Medical dissolution therapy. In: Paumgartner G, Stiehl A, Barbara L, et al., eds. Strategies for the treatment of hepatic biliary disease. Lancaster: Kluwer Academic, 1990:163-80.
41. Philips RS, Barkin JS. Oral dissolution therapy for cholelithiasis: mix and match. Am J Gastroenterol 1990;85:1532-3.
42. Jazrawi RP, Pigozzi MG, Galatola G, et al. Optimum bile acid treatment for rapid gall stone dissolution. Gut 1992;33:381-6.
43. Kupfer RM, Maudgal DP, Northfield TC. Gallstone dissolution rate during chenic acid therapy: effect of bedtime administration plus low cholesterol diet. Dig Dis Sci 1982;27:1025-9.
44. Fedorowski T, Salen G, Tint GS, et al. Transformation of chenodeoxycholic acid and ursodeoxycholic acid by human intestinal bacteria. Gastroenterology 1979;77:1068-73.
45. Pitt HA, McFadden DW, Gadacz TR. Agents for gallstone dissolution. Am J Surg 1987;153:233-46.
46. Senior JR, Johnson MF, DeTurck DM, et al. In vivo kinetics of radiolucent gallstone dissolution by oral dihydoxy bile acids. Gastroenterology 1990;99:243-51.
47. Fromm H. Gallstone dissolution therapy : current status and future prospects. Gastroenterology 1986; 91:1560-7.
48. Northfield TC, Maudgal DP. Oral medical therapy. In: Gallstone disease and its management. Bateson M, ed. Lancaster: MTP Press ltd.,1986:203-27.
49. Palmer AK, Heywood R. Pathological changes in Rhesus monkey fetus associated with oral administration of chenodeoxycholic acid. Toxicology 1974;2:239-46.
50. Ward A, Brogden RN, Heel RC, et al. Ursodeoxycholic acid: a review of its pharmacological properties and therapeutic efficacy. Drugs 1984;24:95-131.

51. Fromm H. Gallstone dissolution with ursodiol: patient selection. Dig Dis Sci 1989;34:36S-38S.
52. Bachrach WH, Hofmann AF. Ursodeoxycholic acid in the treatment of cholesterol cholelithiasis: part 1. Dig Dis Sci 1982;27:737-61.
53. Palma J, Reyes H, Ribalta J, et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Hepatology 1992;15:1043-7.
54. 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.
55. Allen MJ, Borody TJ, Bugliosi TF, et al. Cholelitholysis using methyl tertiary butyl ether. Gastroenterology 1985;88:122-5.
56. Thistle JL, Carlson GL, Hoffman AF, et al. Monooctanoin, a dissolution agent for retained cholesterol bile duct stones: physical properties and clinical application. Gastroenterology 1980;78:1016-22.
57. Igimi H, Tamura R, Toraishi K, et al. Medical dissolution of gallstones. Clinical experience of d-limonene as a simple, safe and effective solvent. Dig Dis Sci 1991;36:200-8.
58. Esch O, Spinosa JC, Hamilton RL, et al. Reversible cytotoxicity to the gallbladder mucosa of contact dissolution solvents for cholesterol gallstones: a comparison of methyl-tert-butyl ether (MTBE) and ethyl propionate (EP) in two animal models. Gastroenterology 1991;100:A315.
59. Schumacher KA, Swobodnik W, Janowitz P, et al. Radiographic aspects in transcatheter contact dissolution of calcified gallbladder concrements. Eur J Radiol 1990;10:28-34.
60. Sonnenberg E van, Casola G, Zakko SF, et al. Gallbladder and bile duct stones: percutaneous therapy with primary MTBE dissolution and mechanical methods. Radiology 1988;169:505-9.
61. Venu RP, Greenen JE, Toouli J, et al. Gallstone dissolution of monooctanoin infusion through an endoscopically placed nasobiliary catheter. Am J Gastroenterol 1982;77:227-30.
62. McNulty J, Chua A, Keating J, et al. Dissolution of cholesterol gall stones using methyltertbutyl ether: a safe effective treatment. Gut 1991;32:1550-3.
63. Zakko SF, Hofmann AF. Microprocessor-assisted solvent-transfer system for gallstone dissolution: in vitro and in vivo validation. Gastroenterology 1990;99:1807-13.
64. Vergunst H, Terpstra OT, Nijs HGT, et al. In vitro comparison of diffferent gall stone dissolution solvents. Gut 1991;32:211-4.
65. Leuschner U, Hellstern A, Wendt T, et al. Endoscopy of the gallbladder as control of gallstone therapy with Methyl-tert-Butyl Ether. Am J Gastroenterol 1988;83:169-72.
66. May GR. Solvent dissolution of gallstones. Radiology 1988;168:331-2.
67. Lu SC. Frontiers of gallstone therapy. How far have we come with nonsurgical methods? Postgrad Med 1989;85:90-2.
68. Leuschner U, Hellstern MD, Schmidt K, et al. Gallstone dissolution with Methyl tert-Butyl Ether in 120 patients. Efficacy and Safety. Dig Dis Sci 1991;36:193-9.
69. Thistle JL. Direct contact dissolution of gallstones. Sem Liver Dis 1987; 7:311-6.
70. Holl J, Sauerbruch T, Sackmann M, et al. Combined treatment of symptomatic gallstones by extracorporeal shock-wave lithotripsy (ESWL) and methyl tert-butyl ether (MTBE). Dig Dis Sci 1991;36:1097-1101.
71. Cushieri A. Non-surgical options for the management of gallstone disease: an overview. Surg Endosc 1990;1:127-31.
72. Chaussy Ch, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980;ii:1265-8.
73. Chaussy CG, 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.
74. Sauerbruch T, Delius M, Paumgartner G, et al. Fragmentation of gallstones by extracorporeal shock waves. N Eng J Med 1986;314:818-22.
75. 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.
76. Coleman AJ, Saunders JE, Crum LA, et al. Acoustic cavitation generated by an extracorporeal shockwave lithotriptor. Ultrasound Med Biol 1987;13:69-76.
77. Delius M, Brendel W, Heine G. A mechanism of gallstone destruction by extracorporeal shockwaves. Naturwissenschaften 1988;75: 200-1.
78. Ferruci JT. Biliary lithotripsy: 1989. AJR 1989;153:15-22.
79. Greiner L, Münks C, Heil W, et al. Gallbladder stone fragments in feces after biliary extracorporeal

shock-wave lithotripsy. Gastroenterology 1990;98:1620-4.
80. Sackmann M, Pauletzki J, Sauerbruch T, et al. The Munich gallbladder lithotripsy study: results of the first 711 patients. Ann Intern Med 1991;114:290-6.
81. Toom R den, Vergunst H, Nijs HGT, et al. Electromagnetic lithotripsy of gallbladder stones: a wide range of inclusion criteria. Am J Gastroenterol 1992;87:497-503.
82. Nealon WH, Urrutia F, Fleming D, et al. The economic burden of gallstone lithotripsy: will cost determine its fate? Ann Surg 213;1991:645-50.
83. Meiser G, Heinerman M, Lexer G, et al. Aggressive extracorporeal shock wave lithotripsy of gall bladder stones within wider treatment criteria: fragmentation rate and early results. Gut 1992;33:277-81.
84. Darzi A, El-Sayed E, O'Morain C, et al. Piezoelectric lithotripsy for gallstones: analysis of results in patients with extended selection. Br J Surg 1991;78:163-6.
85. Rawat BR, Burhenne HJ. Extracorporeal shock wave lithotripsy of calcified stones: work in progress. Radiology 1990;178:667-70.
86. Sackmann M, Pauletzki J, Delius M, et al. Noninvasive therapy of gallbladder calculi with a radiopaque rim. Gastroenterology 1992;102:988-93.
87. Brink JA, Simeone JF, Mueller PR, et al. Physical characteristics of gallstones removed at cholecystectomy: implications for extracorporeal shock-wave lithotripsy. AJR 1988;151:927-31.
88. Vanderpool D, Jones RC, O'Leary JP, et al. Biliary lithotripsy. Am J Surg 1989;158:194-7.
89. Magnuson TH, Lillemoe KD, Pitt HA. How many Americans will be eligible for biliary lithotripsy. Arch Surg 1989;124:1195-1200.
90. Rege RV, Nemcek AA, Nahrwold DL. Selection of patients for gallstone lithotripsy. Am J Surg 1989;158:184-7.
91. 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.
92. Plaisier PW, Hul RL van der, Toom R den, et al. Eligibility for extracorporeal shock wave lithotripsy in 596 consecutive patients attending an outpatient biliary clinic. HPB Surg 1992;5(suppl):83.
93. Mosnier H, Guivarc'h M. Safety and efficacy of piezoelectric extracorporeal lithotripsy (PEL) for gallstones: preliminary results. Hepatology 1988;8:1256.
94. Sackmann M, Niller H, Ippisch E, et al. Gallstone recurrence after lithotripsy. Gastroenterology 1992;102:A332.
95. Picus D, Hicks ME, Darcy MD, et al. Percutaneous cholecystolithotomy: analysis of result and complications in 58 consecutive patients. Radiology 1992;183:779-84.
96. Kellett MJ, Wickham JEA, Russell RCG. Percutaneous cholecystolithotomy. Br Med J 1988;296:453-5.
97. Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy. Endoscopy 1989;21:365-6.
98. Cope C, Burke DR, Meranze SG. Percutaneous extraction of gallstones in 20 patients. Radiology 1990;176:19-24.
99. Chiverton SG, Inglis JA, Hudd C, et al. Percutaneous cholecystolithotomy: the first 60 patients. Br Med J 1990;300:1310-2.
100. Leahy AL, Darzi AW, Murchan PM, et al. A safe new procedure for high-risk patients with symptomatic gallstones. Br J Surg 1991;78:1319-20.
101. Gillams A, Curtis SC, Donald J, et al. Technical considerations in 113 percutaneous cholecystolithotomies. Radiology 1992;183:163-6.
102. Miller FJ, Kensey KR, Nash JE. Experimental percutaneous gallstone lithotripsy: results in swine. Radiology 1989;170:985-7.
103. Miller FJ, Rose SC, Buchi KN, et al. Percutaneous rotational contact biliary lithotripsy : initial clinical results with the Kensey Nash Lithotrite. Radiology 1991;178:781-5.
104. Dubois F, Icard P, Berthelot G, et al. Coelioscopic cholecystectomy. Preliminary report of 36 cases. Ann Surg 1990;211:60-2.
105. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991;324:1073-8.
106. Cuschieri A, Dubois F, Mouiel J, et al. The European experience with laparoscopic cholecystectomy. Am J Surg 1991;161:385-7.

107. Soper NJ, Barteau AJ, Clayman RV, et al. Comparison of early postoperative results for laparoscopic versus standard open cholecystectomy. Surg Gynecol Obstet 1992;174:114-8.
108. Gadacz T, Talamini MA. Traditional versus laparoscopic cholecystectomy. Am J Surg 1991;161:336-8.
109. Graves HA, Ballinger JF, Anderson WJ. Appraisal of laparoscopic cholecystectomy. Ann Surg 1991;213:655-64.
110. Bailey RW, Zucker KA, Flowers JL, et al. Laparoscopic cholecystectomy: experience with 375 consecutive patients. Ann Surg 1991;214:531-41.
111. Davidoff AM, Pappas TN, Murray EA, et al. Mechanisms of major biliary injury during laparoscopic cholecystectomy. Ann Surg 1992;215:196-202.
112. Moossa AR, Easter DW, Sonnenberg E van, et al. Laparoscopic injuries to the bile duct: a cause for concern. Ann Surg 1992;215:203-8.
113. Berci G, Sackier JM, Paz-Partlow M. Routine or selected intraperative cholangiography during laparoscopic choleystectomy. Am J Surg 1991;161:355-60.
114. Flowers JL, Zucker KA, Graham SM, et al. Laparoscopic cholangiography: results and indications. Ann Surg 1992;215:209-16.
115. Gompertz RHK, Rhodes M, Lennard TWJ. Laparoscopic cholangiography: an effective and inexpensive technique. Br J Surg 1992;79:233-4.
116. Petelin JB. Laparoscopic approach to common duct pathology. Surg Laparosc Endosc 1991;1:33-41.
117. Ferzli GS, Massaad A, Ozuner G, et al. Laparoscopic exploration of the common bile duct. Surg Gynecol Obstet 1992;174:419-21.
118. Lexer GW, Lexet GC, Reichenauer A, et al. Laparoscopic cholecystectomy under epidural anesthesia: an ideal combination of minimal invasive surgery and minimal invasive anesthesia. HPB Surg 1992;5(suppl):21.
119. Pace RF, Smith R. Out-patient laparoscopic cholecystectomy. HPB Surg 1992;5(suppl):21.
120. Chang BW, Pollock ME, Eugene J, et al. Experimental cholelitholysis with the pulsed tunable dye laser. J Invest Surg 1991;4:467-76.
121. Hochberger J, Gruber E, Wirtz P, et al. Lithotripsy of gallstones by means of a quality switched giant-pulse neodymium:yttrium-aluminum-garnet laser. Basic in vitro studies using a highly flexible fiber system. Gatroenterology 1991;101:1391-8.
122. Ruppin DC, Dowling RH. Is recurrence rate inevitable after gallstone dissolution by bile acid treatment? Lancet 1982;i:181-4.
123. Lanzini A, Jazrawi RP, Kupfer RM, et al. Gallstone recurrence after medical dissolution; an overestimated threat ? J Hepat 1986;3:241-6.
124. O'Donnel LDJ, Heaton KW. Recurrence and re-recurrence of gallstones after medical dissolution : a long term follow up. Gut 1988;29:655-8.
125. Villanova N, Bazzoli F, Taroni F, et al. Gallstone recurrence after successfull oral bile acid treatment. A 12-year follow-up study and evaluation of long-term postdissolution treatment. Gastroenterology 1989;97:726-31.
126. Schirmer BD, Edge SB, Dix J, et al. Laparoscopic cholecystectomy: treatment of choice for symptomatic cholelithiasis. Ann Surg 1991;213:665-77.

Table 1 : exclusion criteria for the different treatment modalities for symptomatic gallstone disease

	High surgical risk	Acute biliary disease[1]	Stone diameter (mm)	Stone number	Negative OCG[2]	Calcified stones	Pregnancy	Oral Contra-ceptives	Previous UA surgery[3]
OC	±	-	-	-	-	-	±	-	-
OBA	-	+	>15	-	+	+	±[4]	+	-
CD	-	+	-	-	+	+	-	-	-
ESWL	-	+	<5 >30	>3	+	+	+	+	-
PC	±	+	-	-	±	-	±	-	-
RCL	-	+	>25	-	+	-	±	-	±
LC	±	±	-	-	-	-	±	-	±

+ : absolute contra-indication ; - : no contra-indication; ± : relative contra-indication

OCG = Oral Cholecystography, OC = Open Cholecystectomy, OBA = Oral Bile Acid therapy, CD = Contact Dissolution, ESWL = Extracorporeal Shock Wave Lithotripsy, PC = Percutaneous Cholecystolithotomy, RCL = Rotary Contact Lithotripsy, LC = Laparoscopic Cholecystectomy

1: acute biliary disease = acute cholecystitis, pancreatitis, cholangitis, choledocholithiasis, 2: negative OCG = non-opacification of the gallbladder, 3: UA = upper abdominal, 4: see text

Eligibility for extracorporeal shock wave lithotripsy of gallbladder stones using different entry criteria

P.W. Plaisier, R.L. van der Hul, H.G.T. Nijs, R. den Toom, O.T. Terpstra, H.A. Bruining

J Stone Dis 1993;5:125-30

Abstract

Extracorporeal Shock Wave Lithotripsy (ESWL) was introduced as a nonsurgical treatment for uncomplicated, symptomatic gallstone disease. Due to its limited results and the possibility of stone recurrence, ESWL is mainly indicated for patients who reject or cannot tolerate cholecystectomy. For budgetary and planning purposes, it is essential to know what percentage of patients is eligible for this form of therapy. In the literature suitability is either reported variably (ranging from 10 to 53%) or not mentioned. We retrospectively assessed eligibility for ESWL for different entry criteria, based on the histories of 694 consecutive patients, who were referred for gallstone therapy from 1 April, 1988 to 1 October, 1991. Only 10.3-46.9% of symptomatic patients were found eligible for ESWL, depending on the entry criteria used. When the overall results are compared with eligibility, there is no inverse relationship. This suggests that patient selection is not the only factor determining the results of therapy. It is concluded, therefore, that also other factors, such as treatment schemes, the lithotriptors used and experience of the treating physicians, are importants factors for the outcome of ESWL therapy.

Introduction

In 1985 Extracorporeal Shock Wave Lithotripsy (ESWL) was introduced as a noninvasive treatment for uncomplicated, symptomatic gallstone disease [1]. The first results of large series of patients treated with ESWL, were published in 1988 [2]. At first the selection criteria, as used by the Munich group [1-3], were adopted worldwide. However, gradually, the entry criteria for ESWL became less strict [4-15]. Although some authors suggest that proper patient selection is essential for successful ESWL [2,5,16], others consider selection criteria arbitrary [4,8,10,11].

Eligibility for ESWL has been estimated to be between 10.4 and 53.0% [2,3,5,6,10,13,14,17-24]. Obviously, this wide range is a consequence of the fact that various selection criteria are used. Also for other reasons these data cannot be compared directly: various authors calculated eligibility from different patient groups and data were collected in various ways. The aim of this study is to overcome the problem of different definitions and different methods of selection, thus contributing to a better deliniation of the role of ESWL for gallstone management in general, and the need for lithotriptors in particular. Therefore, we calculated eligibility for this treatment modality using various selection criteria. These calculations were based on the clinical findings of 694 consecutive patients, who were referred to our institute for gallstone therapy and correlated the results to the overall results reported by different investigators.

Patients and methods

From 1 April, 1988 tol 1 October, 1991, 694 patients (174 men [25.1%] and 520 women [74.9%]) visited our surgical outpatient clinic for gallstone disease. Four hundred twenty patients (60.5%) were referred by their general physician, 155 (22.3%) by specialists, and 119 (17.1%) visited the clinic on their own initiative. Mean age was 49.1 $\pm$ 15 years (median 48; range: 19-88). Twenty patients (2.9%) had an increased operative risk [ASA-classification III] and 192 were overweight [Quetelet-index >27.0] (27.7%).

All patients were analysed according to protocol. Special attention was paid to symptomatology, concomitant diseases, previous operations, and the patient's preference for therapy. Patients were considered symptomatic according to the Roma working group definition: pain more than 15 minutes and shorter than 5 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 [25].

At physical examination, special attention was paid to patient's height, weight, blood pressure, abdomen, heart and lungs. Laboratory tests consisted of a white blood cell count, serum levels of hemoglobin, total bilirubin, cholesterol, alkaline phosphatase, gamma-glutamyl transpeptidase, aspartate- and alanine aminotransferase and amylase.

On ultrasonography (US) gallbladder size (normal/contracted/hydrops), number of gallstones, diameter of largest stone, gallbladder wall thickening, grit (concrements <3 mm), sludge, stone impaction and enlarged common bile duct were noted, if present. On oral cholecystography (OCG) contrast in gallbladder and/or small bowel, number of gallstones, diameter of largest stone, presence, and extension of calcifications (core/rim/total) and buoyancy (the presence of floating stones) were assessed.

Results of recent examinations done elsewhere were not repeated and used in this study. OCG was not performed, when the patient refused ESWL as a therapeutic option or previous US examination excluded the patient from ESWL according to our own -wide- criteria: 1-10 gallstones with a minimum diameter of 5mm with no calcifications or calcifications of a rim <3mm in symptomatic, non-acute patients with functioning gallbladders [13].

All data were collected retrospectively and eligibility was calculated by exclusion (Figure 1). Eligibility was defined as a percentage of symptomatic patients, who fulfilled the entry criteria for ESWL. The ideal candidate for ESWL, as defined by Sackmann [2,26], was regarded a symptomatic, non-acute patient with one non-calcified gallbladder stone with a maximum diameter of 20mm.

Results

Seventeen patients (2.4%) discontinued analysis: withdrawal from further analysis (12) and emergency cholecystectomy in another hospital (5). One hundred three (14.8%) patients were excluded on history: no biliary symptoms (93), coagulation disorder (2), anti-coagulant medication (2), pregnancy (1) and pregnancy wish (4). One patient turned out to have had a cholecystectomy some 15 years before. Fifty six patients (8.1%) were excluded on concomitant biliary disease: suspected choledocholithiasis (n=46); US proven enlarged common bile duct (26), disturbed liver function [>2x highest normal value] (18), or both (2), or pancreatitis (10). Ninety eight patients (14.1%) were excluded for ESWL, because they preferred cholecystectomy. One hundred and fifty-five patients (22.3%) were excluded

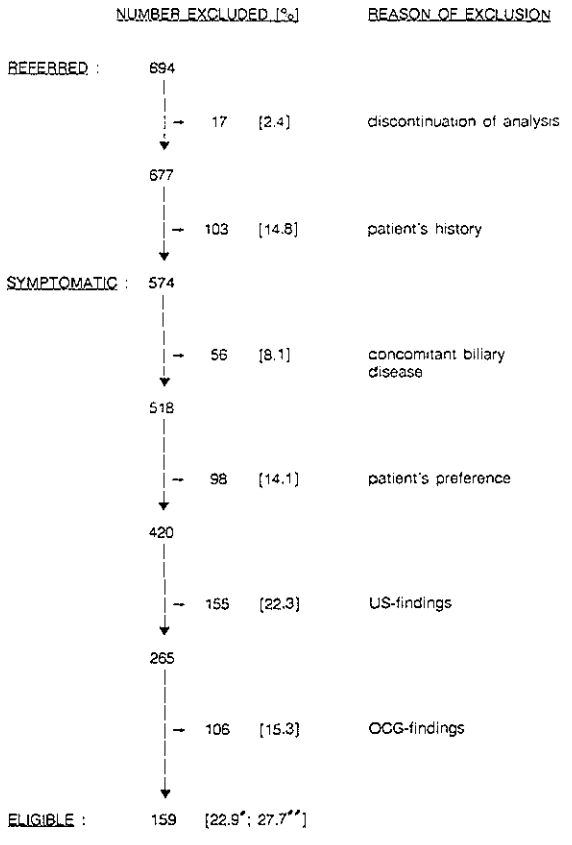

Figure 1: flow chart for determining eligibility for ESWL

#) percentage of referred population

##) percentage of symptomatic population

1) ultrasonography

2) oral cholecystography

on US-findings: more than 10 stones (122), no stones (24), diameter of gallstones <5mm (9). Another 106 patients (15.3%) were excluded on OCG-findings; non-functional gallbladder (65) and calcifications more than a rim (41). Of the patients with no stones, 9 had polyps, 4 a pathological gallbladder wall thickening or adenomyomatosis and 11 probably passed their stones. No patients were excluded due to cysts, aneurysms or lung tissue in the shock wave path.

Table1 : calculated and reported eligibility for ESWL

first author (ref.)	maximum diameter (mm)	maximum number	maximum calcification	% eligible calculated in this study	% eligible reported by authors
Sackmann (15)	30	1	rim	**13.4**	-
Sackmann(2)	30	3	any	**17.2**	28
Sackmann (3)					19
Brink (17)					15
Magnuson (18)					19
Rege (20)	30	3	rim	**19.7**	45
Ponchon (7)	25-35[a]	10	any	**20.7**	25
Den Toom (13)	-	10	rim	**27.7**	30
Vanderpool (5)	20	-	any	**30.1**	10
Rawat (9)	-	10	-	**30.7**	-
Zeman (10)	-	-	rim	**34.0**	53
Darzi (11)	30[b]	-	any[b]	**46.9**	-
Ideal	20	1	any	**10.3**	-

a : only an exclusion-criterion if combined

b: maximum diameter depending on number of stones

Of the original 694 patients, 159 patients (22.9 %) were eligible for ESWL using our selection criteria [13], representing 27.7% of 574 symptomatic patients (Figure 1). Eligibility for different selection schemes from other authors is depicted in Table 1. Overall results in relation to calculated and reported eligibility are shown in Figure 2.

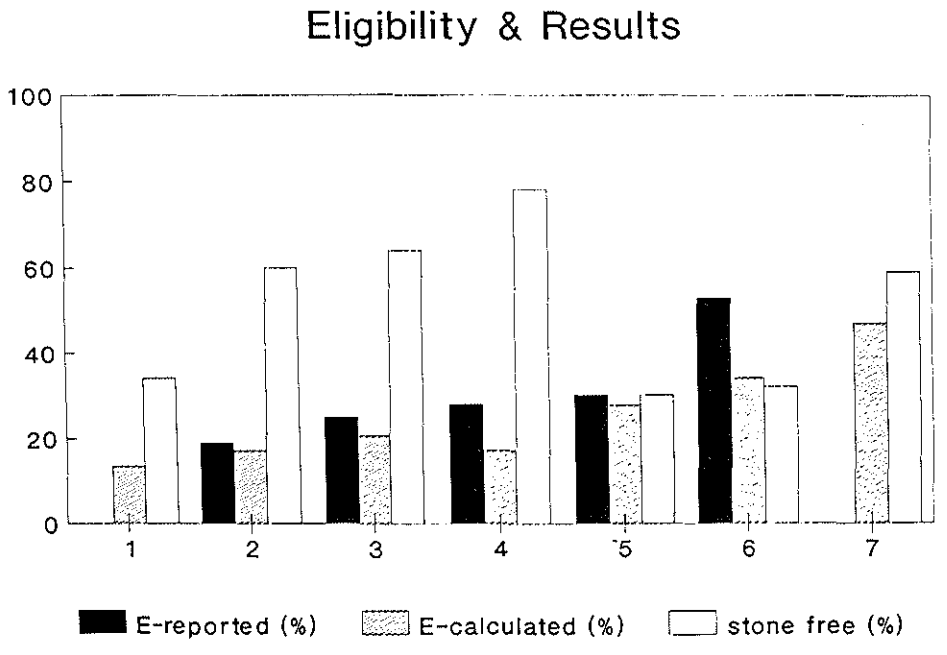

Figure 2: ESWL: results and eligibility

1: Sackmann (ref. #15), 2 : Sackmann (ref. #3), 3: Ponchon (ref. #7), 4: Sackmann (ref. #2), 5: Den Toom (ref. #13), 6: Zeman (ref. #10), 7: Darzi (ref. #11); E = eligibility

Discussion

We calculated eligibility for different selection schemes, because the data reported cannot be compared directly. Data cannot be compared for several reasons. Different authors defined 'eligibility' in various ways and collected data in different ways. Some defined eligibility as a percentage of a referred population [2,3], and others as a percentage of symptomatic patients [13,18]. Sackman et al. [2,3] used pre-treatment radiologic findings, Brink and co-workers [17] used contents of extirpated gallbladders and Magnuson [18] used both. Selection

of the material of patients again renders these studies incomparable [18]: patients were referred for gallstone management [13,17], primarily for ESWL [2,3,6,10,22] or contacted directly for possible ESWL [5].

Eligibility for different entry criteria, as calculated by us in 574 symptomatic gallstone patients, varies from 17.2-46.9% (Table 1). These data are more or less in accordance with the eligibility in the literature, as reported by different authors [2,3,5,6,10,13,14,17-24]. Our data could be applied to all selection schemes without reservations except those three that did not use the number of stones as an exclusion criterion [5,10,11]. As we regard 10 stones as the upper limit for ESWL, we did not perform an OCG, if US revealed >10 stones. Although in 122 patients US revealed >10 stones, in 78 cases an OCG was in fact available, either because other specialists had them ordered, or because US and OCG were performed combined on the same day. Of the 44 patients without OCG, 31 were eligible (70%) for ESWL using the Darzi and the Vanderpool scheme [5,11], representing those patients expected to have a functioning gallbladder, without calcifications more than a rim. We did not include these 31 patients in the Zeman scheme [10]: although Rege and co-workers [20] did not use the number of stones as an exclusion criterion, they excluded patients on number of gallstones, when the total stone load exceeded 50% of the gallbladder volume. Because we were not informed of gallbladder volume, we did not regard the 31 patients, expected to have functioning galbladders and gallstones without calcifications of more than a rim eligible for ESWL. For the aforementioned reasons, especially our calculated eligibility for the Zeman scheme must be regarded with caution.

The most striking discrepancy between reported and calculated eligibility is present in the schemes of Rege [20] and Vanderpool [5]. Preselection is a possible explanation for the difference between our calculated data and the data reported by Rege, for their entry criteria differ only from the Sackmann-scheme [2,3] with respect to the presence of a calcified rim, explaining the extra 2.5% of symptomatic patients eligible for ESWL. The discrepancy between our data and Vanderpool's are most likely due to the fact that many of his patients failed to pursue evaluation [5].

Our patient group largely represents the general gallstone population because the traditional risk factors for gallstone disease (female, fat, forty) are highly retrievable, despite a large number of asymptomatic patients (n=93 [13.4%])- a number much larger than reported elsewhere (6% [2], 5% [20]). It is, however, not likely that this phenomenon has

influenced eligibility, for we defined eligibility as a percentage of symptomatic (not: 'referred') patients. Also, no differences in patient characteristics could be demonstrated between the symptomatic group and the asymptomatic group.

A considerable number of patients refused ESWL as a therapeutic option. Although this may have lead to selection, this selection influenced all calculations to the same extent. It is of special interest that in 11 patients with a clear history of biliary colic, no stones or other gallblader abnormalities could be demonstrated, as was reported previously [20].

Narrowing of entry criteria, which should logically go together with a reduced eligibility, is surprisingly not automatically accompanied by improvement of the results (Figure 2). This is the case for both our calculated data and the suitability reported. Therefore, we conclude that selection criteria play only a partial role in determining the overall results of ESWL. Although it has been established that size, number, and gallstone composition are major determinants of the time of complete clearance [2,20,27], overall results must also be dependent on other factors: the lithotriptor used, the treatment scheme (number of shock waves and/or energy settings), or the experience of the physicians. Studies comparing the results of different lithotriptors [3,15,28] or the results of different treatment schemes [3,15] are warranted to further investigate this conclusion. Although relevance of overall results as a parameter of ESWL has been discussed previously [20], our data support the idea that perhaps only results for 'ideal patients' should be considered instead of overall results.

Our data confirm that ESWL is applicable in only the minority of symptomatic gallstone patients. Moreover, we found that only 10.3% of symptomatic patients can be considered 'ideal' for ESWL (Table 1). Our data also confirmed that US should be the first procedure, when screening for ESWL. US is safe and rather accurate in assessing stone load (number and diameter of gallstones). If stone load, as assessed by US, does not exceed the maximum number, the next step should be an OCG, on which patency of the cystic duct and calcifications of stones can be assessed. When the number of stones is abandoned as an exclusion criterion, one could consider to have an OCG performed directly.

Apart from its limited results, the need for adjuvant therapy (with its disadvantages) [29], and the possibility of stone recurrence [30], ESWL has also a limited applicability (Table 1). ESWL will play a less important role than previously thought [31,32]. Its main indication will be those symptomatic gallstone patients, who cannot or are unwilling to be operated upon.

References

1. Sauerbruch T, Delius M, Paumgartner G, et al. Fragmentation of gallstones by extracorporeal shock waves. N Eng J Med 1986;314:818-22.
2. 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.
3. Sackmann M, Pauletzki J, Sauerbruch T, et al. The Munich gallbladder lithotripsy study: results of the first 711 patients. Ann Intern Med 1991;114:290-6.
4. Darzi A, Monson JRT, O'Morain C, et al. Extension of selection criteria for extracorporeal shock wave lithotripsy for gall stones. Br Med J 1989;299:302-3.
5. Vanderpool D, Jones RC, O'Leary JP, et al. Biliary lithotripsy. Am J Surg 1989;158:194-7.
6. Albert MB, Fromm H, Shehan CM, et al. Preliminary U.S. experience with the EDAP LT01 piezoelectric lithotriptor in treating gallstones. Gastroenterology 1989;96:A570.
7. Ponchon T, Barkun AN, Pujol B, et al. Gallstone disappearance after extracorporeal lithotripsy and oral bile acid dissolution. Gastroenterology 1989;97:457-63.
8. Albert MB, Fromm H, Shenan CM. Densely calcified gallstone treated successfully with piezoelectric lithotripsy. Gastroenterology 1990;98:777-9.
9. Rawat BR, Burenne HJ. Extracorporeal shock wave lithotripsy of calcified gallstones: work in progress. Radiology 1990;175:667-70.
10. Zeman RK, Davros WJ, Goldberg JA et al. Gallstone lithotripsy: results when number of stones is exlcuded as a criterion for treatment. AJR 1991;157;747-52.
11. Darzi A, El-Sayed E, O'Morain C, et al. Piezoelectric lithotripsy for gallstones: analysis of results in patients with extended selection. Br J Surg 1991;78:163-6.
12. Torres WE, Steinberg HV, Davis RC, et al. Extracorporeal shock wave lithotripsy of gallstones: results and 6-month follow-up in 141 patients. Radiology 1991;178:509-12.
13. Toom R den, Vergunst H, Nijs HGT, et al. Electromagnetic lithotripsy of gallbladder stones using a wide range of inclusion criteria. Am J Gastroenterol 1992;87:497-503.
14. Meiser G, Heinerman M, Lexer G, et al. Agressive extracorporeal shock wave lithotripsy of gall bladder stones within wider treatment criteria: fragmentation rate and early results. Gut 1992;33:277-81.
15. Sackmann M, Pauletzki J, Delius M, et al. Noninvasive therapy of gallbladder calculi with a radiopaque rim. Gastroenterology 1992;102:988-93.
16. Schnegg JF, Thorens J, Fasel J et al. Extracorporeal shock wave lithotripsy in unselected gall-stone patients. Gastroenterology 1989;96:A656.
17. Brink JA, Simeone JF, Mueller PR, et al. Physical characteristics of gallstones removed at cholecystectomy: implications for extracorporeal shock-wave lithotripsy. AJR 1988;151:927-31.
18. Magnuson TH, Lillemoe KD, Pitt HA. How many Americans will be eligible for biliary lithotripsy? Arch Surg 1989;124:1195-1200.
19. Way LW. Trends in the treatment of gallstone disease: putting the options into context. Am J Surg 1989;158:251-3.
20. Rege RV, Nemcek AA, Nahrwold DL. Selection of patients for gallstone lithotripsy. Am J Surg 1989;158:184-7.
21. Freund HR, Lebensart PD, Muggia-Sullam M, et al. Extracorporeal shock wave lithotripsy (ESWL) of gallbladder stones: selection of patients and prelimanary results. Gastroenterology 1989;96:A598.
22. Brunner H, Schneider G, Boehmig HJ, et al. How many patients with cholecystolithiasis are candidates for extracorporeal shock wave lithotripsy or dissolution with methyl-tert-butyl ether (MTBE)? Gastroenterology 1989;96:A580.
23. Cushieri A. Non-surgical options for the management of gallstone disease: an overview. Surg Endosc 1990;4:127-31.
24. Desmond PV. Current options for the management of gallstones. Med J Aust 1991;154:400-1 & 404-6.
25. 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.
26. Maher JW, Summers RW, Dean TR, et al. Early results of combined electrohydraulic shock-wave lithotripsy and oral litholytic therapy of gallbladder stones at the University of Iowa. Surgery 1990;108:648-54.

27. Barkun ANG, Ponchon T. Extracorporeal biliary lithotripsy: review of experimental studies and a clinical update. Ann Intern Med 1990;112:126-37.
28. Schneider HT, Fromm M, Ott R, et al. In vitro fragmentation of gallstones: comparison of electrohydraulic, electromagnetic piezoelectric shockwave lithotripters. Henatology, 1991;14:301-5.
29. Fromm H. Gallstone dissolution therapy: current status and future prospects. Gastroenterology 1986;91:1560-7.
30. Sackmann M, Ippisch E, Sauerbruch T, et al. Early gallstone recurrence after successful shock wave therapy. Gastroenterology 1990;98:392-6.
31. Maglinte DDT, Graffis R, Jordan L, et al. Extracorporeal shock wave lithotripsy of gallbladder stones: a pessimistic view. Radiology 1990;178:29-32.
32. Zeman RK, Al-Kawas F, Benjamin SB. Gallstone lithotripsy: is there still cause for optimism? Radiology 1991;178:33-5.

CHAPTER 4

Gallstone lithotripsy: the Rotterdam experience

P.W. Plaisier, R.L. van der Hul, R. den Toom, H.G.T. Nijs, O.T. Terpstra, H.A. Bruining

Hepatogastroenterol (accepted for publication)

Abstract

In the period September 1988 - September 1992, 133 patients (34 ♂ and 99 ♀; mean age: 49 years [range 24-81]) underwent 299 ESWL-sessions with adjuvant oral bile acid therapy. Mean number of ESWL-sessions was 2.5 (1-7), mean number of shock waves was 2817 (75-4000) and mean duration per session was 62 minutes (35-210). Ninety eight patients (73.7%) required intravenous analgo-sedation. At last follow-up (mean: 17.7 months [2-46]), 37 patients (27.8%) are free of stones and 30 (22.6%) underwent cholecystectomy. At 1 year after the first ESWL-session, 51.0% of the patients with a solitary stone and 8.3% of the patients with 2-10 stones are free of concrements ($p<0.0001$). Fourteen per cent (6/43) of the patients developed recurrent stones. Major complications comprised pancreatitis ($n=4$; 3.0%) and acute cholecystitis ($n=1$; 0.8%). Our results reconfirm that ESWL is safe and moderately effective in selected patients. Because of the wide acceptance of the laparoscopic cholecystectomy, ESWL shall be confined to patients with an increased operative risk and patients, who refuse surgery. Considering the poor results in multiple stones, ESWL should be confined to solitary stones.

Introduction

Extracorporeal shock wave lithotripsy (ESWL) with adjuvant oral bile acid therapy is a non-invasive treatment modality for symptomatic gallstone disease. After ESWL displaced surgical therapy of urinary stones, it was introduced in gastroenterology in 1985 [1]. The initial results were very promising [2] and inspired us to also use ESWL in our hospital. Here, we present our experience in 133 patients.

Patients and methods

Our entry criteria for ESWL are depicted in Table 1.

Table 1 : entry criteria for extracorporeal shock wave lithotripsy

inclusion criteria
Symptomatic gallbladder stones (last biliary colic less than 2 yr ago).
Visualisation of the gallbladder on OCG.
Up to 10 stones on US, no upper limit for stone diameter.
Diameter of the largest stone ≥5mm on US.
Radiolucent stones or small calcified rim (<2mm) on OCG.
exclusion criteria
Acute biliary disease (cholecystitis, jaundice, cholangitis, pancreatitis, hepatitis, or concomitant 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.
ASA III/IV.
Not capable to fulfil follow up.

OCG = oral cholecystography, US = ultrasonography, ASA = classification of operative risk according to the American Assiociation of Anesthesiologists; yr = years

In the period September 1988 - September 1992, 133 patients were treated with ESWL. Patient and stone characteristics are depicted in Table 2. Patients were analyzed at an outpatient clinic according to protocol: patient history, physical examination and -if patients were symptomatic according to the GREPCO definition [3]- laboratory tests and radiologic examination. All patients were treated with the Lithostar plus^{r} (Siemens, Erlangen, Germany), a second generation shockwave lithotriptor, working on the electromagnetic principle.

Table 2 : characteristics of 133 ESWL patients and their gallstones

a. patients

	Mean	Range
Age (years)	49	24 - 81
♂/♀-ratio	0.34 (34/99)	

b. gallstones

	Number	Percentage	
1 stone	70	52.6	
2-5 stones	55	41.4	
6-10 stones	8	6.0	
radiolucent	105	78.9	
calcified rim (≤2mm)	28	21.1	
mean diameter (mm)	17		5-40

Except the first 16 patients, all ESWL sessions were performed on an outpatient basis. Session characteristics are depicted in Table 3. Seven sessions had to be stopped. In one case because the treatment was too painfull despite maximum analgo-sedation and in 6 cases because of a technical failure.

Table 3 : characteristics of 299 lithotripsy sessions in 133 symptomatic gallstone patients

	Number (%)	Mean	Range
Number of ESWL sessions		2.5	1-7
Number of shock waves		2817	75-4000
Session time (min)		61.7	35-210
Requiring anesthesia	98 (73.7)		
*Fentanyl^{r} (mg)		0.102	0.025-0.300
*midazolam (mg)		3.3	0.3 - 15.0
Positioning			
*supine	80 (26.8)		
*left oblique	185 (61.8)		
*both	34 (11.4)		

Adjuvant treatment with oral bile acids (OBA) consisted of a combination of urso- and chenodeoxycholic acid (7-8 mg/kg body weight), taken as a bedtime dose, starting the day after the first ESWL session. Ultrasonography was performed 10 days after each ESWL session, each 3 months and once per year if the patient was free of concrements. Patients were considered stone free, if two consecutive ultrasound examinations could not demonstrate any concrements.

Median and mean follow-up were both 17.7 $\pm$ 11 months (range : 2-46); it should be noted that follow-up stopped when a patient underwent cholecystectomy. The results of 14 patients, treated in the period April - September 1988, were excluded from analysis since they were treated with another machine. Statistical analysis was performed with a standard test for comparing proportions assuming binomial distributions.

Results

The results at final follow-up are depicted in Table 4.

Table 4 : results at last follow-up in 133 patients treated with ESWL

	Number	Percentage
no fragmentation	8	6.0
decrease in diameter largest stone $<25\%$	12	9.0
decrease in diameter largest stone $25\% < x < 50\%$	7	5.3
decrease in diameter largest stone $>50\%$	21	15.8
grit (all concrements <3mm)	12	9.0
free of concrements with ESWL and OBA	37	27.8
cholecystectomized	30	22.6
stone recurrence	6	4.5
total	133	100

ESWL = extracorporeal shock wave lithotripsy; OBA = oral bile acid therapy.

Analysis of the results at 1 year after the first ESWL-session are as follows. The overall stone free rate is 27.9% (31/111). The stone free rates of patients with solitary stones and 2-10 stones are 51.0% (26/51) and 8.3% (5/60), respectively ($p<0.0001$). Stone free rates of patients with radiolucent stones and stones with a calcified rim are 30.9% (29/94) and 11.9% (2/17), respectively ($p=0.10$). Of the patients with stones with a diameter $\leq$20mm and >20mm, eventually 30.9% (30/97) and 16.7% (6/36) became free of stones ($p=0.10$).

Of 43 patients, who had ever become free of stones, 6 (14.0%) developed recurrent stones. In all cases the stones recurred within 12 months after discontinuation of OBA therapy. Only one patient had stone recurrence after treatment of a single stone; the others had multiple stones, before ESWL. In 4 cases the recurrent stones were a-symptomatic and not treated. In 2 patients they caused biliary colics and these patients were treated with oral bile acids (1x) and cholecystectomy (1x). ESWL-related complications are depicted in Table 5, another 15 (11.3%) patients suffered from OBA-related diarrhea. In all cases, the complaints vanished after reducing the dose of chenodeoxycholic acid.

Table 5 : complications in 133 patients treated with ESWL

	Number	Percentage
Colics	57	42.9
Common bile duct obstruction	9	6.8
jaundice/white stool	5	3.8
pancreatitis	4	3.0
Hematuria	2	1.5
Acute cholecystitis	1	0.8
Total	69	50.4

Discussion

Cholecystectomy is the unchallenged standard treatment for symptomatic gallstones [4,5]. Although gallbladder extirpation is more or less a routine operation, it harbors considerable morbidity and mortality rates, 10-30% and 0.1-0.3%, respectively [4,6]. These rates together with the considerable costs accompanying cholecystectomy, were the reason for extensive

research in alternative, preferably non-invasive treatment modalities for gallstone disease [7]. Of these alternatives, ESWL is applied most.

In 1988, the first large series of patients treated with ESWL appeared in the New England Journal of Medicine [2]. The results were very promising, since -at a minimal complication rate- 30, 48, 63, 78 and 91% of the patients became free of stones at 0-2, 2-4, 4-8, 8-12 and 12-18 months, respectively. Eventually, it became evident that the initial results could not be reproduced [8-10], not even by the Munich group [11].

Our overall results are lower and our cholecystectomy rate higher than in other reports [8-11]. Our low overall stone free rate is most probably due to our wide entry criteria. Our results in solitary stones are highly acceptable. Our high cholecystectomy rate is definitely caused by the introduction and consequent acceptance of laparoscopic cholecystectomy [5]. The fact that the differences in the results of the different stone types were not statistically significant, is probably a type II-error caused by small numbers: the differences were indeed evident. Moreover, the significances were demonstrated convincingly elsewhere [12,13].

Our recurrence rate and our finding that most recurrent stones remained a-symptomatic is in accordance with the literature [14]. Also that stone recurrence is more frequent after treatment of multiple stones than of solitary stones, has been reported earlier [15].

We conclude that ESWL is relative effective and safe in selected patients. In general practice, however, ESWL is surpassed by laparoscopic cholecystectomy. As a result, ESWL shall be confined in the future, to patients with a high operative risk and patients who refuse surgery. Considering the reasonable results in patients with solitary stones and the low major complication rate, this seems justified. ESWL should be confined to solitary stones.

References

1. Sauerbruch T, Delius M, Paumgartner G, et al. Fragmentation of gallstones by extracorporeal shock waves. N Eng J Med 1986;314:818-22.
2. 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.
3. 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.
4. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989;158:174-8.
5. Schirmer DB, Edge SB, Dix J, et al. Laparoscopic cholecystectomy: treatment of choice for symptomatic cholelithiasis. Ann Surg 1991;213:665-77.
6. McSherry CK, Glenn F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. Ann Surg 1980;191:271-5.
7. Vergunst H, Terpstra OT, Brakel K, et al. Extracorporeal shock wave lithotripsy of gallstones: possibilities and limitations. Ann Surg 1989;210:565-75.

8. Ponchon T, Barkun AN, Pujol B, et al. Gallstone disappearance after extracorporeal lithotripsy and oral bile acid dissolution. Gastroenterology 1989;97:457-63.
9. Darzi A, El-Sayed E, O'Morain C, et al. Piezoelectric lithotripsy for gallstones: analysis of results in patients with extended selection. Br J Surg 1991;78:163-6.
10. Meiser G, Heinerman M, Lexer G, Boeckl O. Agressive extracorporeal shock wave lithotripsy of gall bladder stones within wider treatment criteria: fragmentation rate and early results. Gut 1992;33:277-81.
11. Sackmann M, Pauletzki J, Sauerbruch T, et al. The Munich gallbladder lithotripsy study: results of the first 5 years with 711 patients. Ann Intern Med 1991;114:290-6.
12. Schoenfield LJ, Berci G, Carnovale RL, et al. The effect of ursodiol on the efficacy and safety of extracorporeal shock- wave lithotripsy of gallstones : The Dornier National Biliary Lithotripsy Study. N Engl J Med 1990;323:1239-45.
13. Elewaut A, Crape A, Afschrift M, et al. Results of extracorporeal shock wave lithotripsy of gall bladder stones in 693 patients: a plea for restriction to slitary stones. Gut 1993;34:274-8.
14. Sackmann M, Ippisch E, Sauerbruch T, et al. Early gallstone recurrence after succesful shock wave therapy. Gastroenterology 1990;98:392-6.
15. Villanova N, Bazzoli F, Taroni F, et al. Gallstone recurrence after successfull oral bile acid treatment. A 12-year follow-up study and evaluation of long-term postdissolution treatment. Gastroenterology 1989;97:726-31.

The course of biliary and gastrointestinal symptoms after treatment of uncomplicated symptomatic gallstones: results of a randomized study comparing extracorporeal shock wave lithotripsy with conventional cholecystectomy

P.W. Plaisier, R.L. van der Hul, H.G.T. Nijs, R. den Toom, O.T. Terpstra, H.A. Bruining

Am J Gastroenterol (accepted for publication)

Abstract

A randomized study was performed comparing extracorporeal shock wave lithotripsy (ESWL) with conventional cholecystectomy for uncomplicated symptomatic gallstones. The primary outcome of the study was the influence of therapy on biliary colics and gastrointestinal symptoms. In the period October 1989 - March 1992, 26 patients were randomized for cholecystectomy and 23 for ESWL. Pain diaries and symptom questionnaires were taken before, and 3, 6, 12, 18 and 24 months after therapy. ESWL patients regularly underwent ultrasound examination for determining stone clearance. Median follow-up was 18 months (12-24). Biliary colics were cured in 90.9% and 45.4% of the patients within 3 months after cholecystectomy or ESWL, respectively ($p < 0.01$). Trend analysis showed that both fatty food upset and stomach swelling improved significantly after cholecystectomy, while nausea improved after ESWL. In five other gastrointestinal symptoms, no significant differences could be detected. It is concluded that cholecystectomy is superior to ESWL in improving biliary colics, fatty food upset and stomach swelling. Since ESWL is, furthermore, not able to clear all stones and harbours the possibility of stone recurrence, cholecystectomy remains the preferred treatment modality in healthy patients with uncomplicated symptomatic gallstones.

Introduction

The initial results of ESWL of gallbladder stones were very promising [1,2]. The fact that all studies on ESWL were observational, inspired us to conduct a randomized trial comparing ESWL of gallstones with conventional cholecystectomy, the gold standard [3].

We considered that the outcome of such a study should be measured in terms of biliary colics and not merely in stone clearance, since biliary colics are considered a manifestation of uncomplicated biliary stone disease. We also evaluated the course of eight gastrointestinal complaints in the two treatment arms.

The aim of this study was to compare the frequency and severity of biliary pain and gastrointestinal complaints after ESWL with those after open cholecystectomy.

Patients and methods

In the period October 1989 - March 1992, 491 patients visited our surgical outpatient gallstone clinic. Asessment for eligibility was according to protocol: a history was taken and a physical examination was performed. Patients were diagnosed as either 'symptomatic' or 'a-symptomatic', using the GREPCO-definition [4]. Asymptomatic patients were excluded immediately and did not receive therapy (n=80).

Symptomatic patients underwent further analysis: laboratory tests and radiological examination. Objective of this analysis was to exclude patients with local and general complications of gallstone disease, such as bile duct stones, pancreatitis, gallbladder polyps, mucoceles and nonfunctioning gallbladders. These patients were excluded because these conditions require a therapy other than ESWL and, therefore, could not be included in the study. So, laboratory tests consisted of liver function tests, serum amylase and a white blood cell count. Radiological examination consisted of ultrasonography (US) and oral cholecystography (OCG). An OCG was not performed if the patient refused ESWL as a therapeutic option or if a previous US examination already excluded the patient from our entry criteria for ESWL (Chapter 4; Table 1). At the end of analysis, all eligible patients (n=87), were informed about the study and were asked for consent to be randomized.

Randomization was stratified on number of stones (1, 2-5, 6-10), so that patients were randomly divided into one of the two treatment groups on a 1:1 basis. The randomization procedure was computerized and performed at the trial office immediately after the consent for randomization was given. Forty-nine patients (56.3%) consented in randomization. Their

characteristics are depicted in Table 1. After a 6 month-intake period, in which no patient could be randomized, intake was stopped in March 1992.

Table 1: patient characteristics of 49 randomized patients in a study comparing extracorporeal shock wave lithotripsy with conventional cholecystectomy

	E-group	C-group
age [years]	50.3 ± 12.5	49.8 ± 12.8
range	32 - 75	30 - 74
♂/♀-ratio	4/19	6/20
Q-index >27.0 (%)	26.1	27.3
1 stone	13	12
2-5 stones	9	12
6-10 stones	1	2
total number of patients	23	26

E-group : extracorporeal shock wave lithotripsy-group

C-group : cholecystectomy-group

Q-index : Quetelet-index [weight (kg)/length $(m)^2$].

ESWL

Shock wave therapy was performed with the Lithostar Plus® (Siemens AG, Erlangen, Germany), a second generation lithotriptor, working on the electromagnetic principle. Treatment was performed at maximal energy level (level 9) and the patients were treated in left oblique or supine position. ESWL was performed as an outpatient procedure. ESWL patients were adjuvantly treated with oral bile acids (OBA) in a combination of urso- and chenodeoxycholic acid (7-8 mg/kg body weight). OBA medication was taken as a bedtime dose, starting the day after the first ESWL session. US was performed 1-2 weeks after each ESWL session and 3, 6, 12, 18, 24 months after the first ESWL-session. If US revealed stones with a diameter >5mm, another ESWL-session was performed as soon as possible (usually within 1 week after this US). If concrements larger than 5mm were found after 3 ESWL-sessions, the patient was advised to undergo cholecystectomy. Patients were considered stone free, if two consecutive US examinations, with an interval of 3 months, could not demonstrate any concrements. After the second US that could not demonstrate concrements, OBA-medication was stopped.

Cholecystectomy

Cholecystectomy was performed by laparotomy, via a subcostal incision. It was performed under general anesthesia, as an inpatient procedure. Intra-operative cholangiography was not performed routinely.

Follow-up

Follow-up consisted of self-administered so-called 'pain diaries' covering the periods 0-3, 3-6, 6-12 and 12-18 months. When patients experienced biliary colics, they had to fill out the date, the duration and severity (mild, moderate or severe) on these diaries. Analogously to the definition of biliary colic, only pain epsiodes longer than 30 minutes were considered.

The patients also self-administered questionnaires, taken before therapy (t=0) and at 3, 6, 12, 18 and 24 months after therapy. On these questionnaires, the patients had to score whether they suffered from the following gastrointestinal complaints: nausea, fatty food upset, vomiting, stomach swelling, pyrosis, belching, constipation and diarrhea. Scoring was performed on a semi-quantative scale (absent, mild, moderate or severe). Both questionnaires and pain diaries were sent by mail in all patients and double-checked 1 month after receipt. Double-checking was performed by interviews, taken at the outpatient clinic for ESWL-patients. In the cholecystectomy-group, the first 5 patients were checked at the outpatient clinic and the next 5 by telephone. Since no differences were found between patients checked at the outpatient clinic and patients interviewed by telephone, the remainder of the cholecystectomy-patients (n=16) were checked by phone.

Statistics

Statistical analysis was done with the Chi-square test (McNemar version), the Chi-square test for trend, the semi-quantative test of Yates-Cochran and the test for comparing proportions assuming binomial distributions. Analyses of the pain diaries and the symptom questionnaires were performed on an intention-to-treat basis. Analysis of the efficacy of ESWL in terms of stone clearance were per protocol, i.e. based on the data of all patients undergoing ESWL.

Results

Forty-nine patients were randomized, 23 for ESWL (E-group) and 26 for cholecystectomy (C-group). Four patients expressed second thoughts after they had initially consented in

randomization. These patients were all C-group patients. Median follow-up was 18.0 months (range : 12-24). No patient was lost to follow-up.

ESWL

Since four patients, who were randomized to cholecystectomy, preferred ESWL, eventually 27 patients underwent lithotripsy. Fourteen patients had a solitary stone and 13 had 2-10 stones at baseline. Mean number of ESWL-sessions was 2.3 $\pm$ 1.0 (median : 2; range: 1-4). Mean number of shock waves per session was 2882 $\pm$ 394 (median : 3000; range: 1225-3500). At 18 months follow-up, 13 patients (48%) were free of stones, 2 (7%) had minimal debris (concrements $<$3mm) and 6 (22%) still had concrements. Another 6 patients (22%) had undergone cholecystectomy because of persistent biliary colics (n=4), acute cholecystitis (n=1) and pancreatitis (n=1). The 2 patients with complications after ESWL, were both operated within 3 months after the first ESWL-session. The 4 patients who were operated because of unsuccessful ESWL, were all operated within 12-15 months after the first lithotripsy. Of the 14 patients with solitary stones at baseline, 9 (64%) eventually became free of concrements, 3 (21%) still have concrements and 2 (14%) were operated after ESWL. Of the 13 patients with multiple stones, these figures were 4 (31%), 5 (38%) and 4 (31%), respectively. The differences in likelihood to become free of stones or operated, were not statistically significant: p=0.08 and p=0.30, respectively. Of the 13 patients who became free of concrements after ESWL, one (8%) developed recurrent symptomatic stones that were successfully treated with OBA. Overall median duration of OBA-treatment was 8 months (range 1-24). Median duration of OBA-treatment in the subgroup of patients, who eventually became free of concrements by ESWL, was 6 months (range : 3-18). In no case OBA's had to be stopped because of abdominal discomfort, rising liver function tests or elevated serum-cholesterol. There was no mortality after ESWL.

Cholecystectomy

Twenty-two patients underwent conventional cholecystectomy as the first procedure. There was no mortality. Median hospitalization time, including the days of admission and discharge, was 8 days (range : 4-12). Another 6 patients underwent cholecystectomy secondary to ESWL. Median hospitalization time in this group was 7.5 days (range : 4-35) and cholecystectomy was performed laparoscopically in 5 patients. The patient who

developed pancreatitis accounted for the hospitalization time of 35 days and she had a conventional cholecystectomy with intraoperative cholangiography. Postoperatively, one patient had to be observed for 6 hours at an intensive care unit for an epileptic insult. Eight months after cholecystectomy, one patient was re-admitted because of common bile duct stones. Hospitalization time was 8 days and the patient was successfully treated with papillotomy and endoscopic extraction. One patient suffered from wound dehiscence, treated conservatively. Two patients complained of persistent scar pain.

Pain diaries and symptom questionnaires

Questionnaires and pain diaries were returned and filled out correctly in 92.7% and 89.8%, respectively.

a. pain diaries

The number of patients complaining of biliary colics after treatmen. are depicted in Table 2. Colics were reported less frequently directly after cholecystectomy, while after ESWL they remained present in about half the cases for the first 3 months ($p<0.01$). Thereafter, a marked improvement occurred in the period 3-6 months in the E-group. Compared to 0-3 months, this improvement was statistically significant ($p<0.001$). After 6 months, no decrease in frequency in biliary colics could be demonstrated in both groups. Overall, a clear trend of improvement was found in the E-group ($p<0.001$). No trend could not be demonstrated in the C-group, because the colics were already cured immediately after treatment. During follow-up, 14 patients reported colics: 2 after cholecystectomy and 12 after ESWL. Of these 12 ESWL-patients, 11 had stones demonstrated at US, while in 1 patient no stones could be demonstrated. Of the patients with biliary colics after cholecystectomy, one had common bile duct stones. The other was treated expectantly at her request. She did not have elevated liver function tests.

b. symptom questionaires

The reported frequencies of fatty food upset, nausea and stomach swelling are depicted in Table 3.

Table 2: The number of patients complaining of moderate or severe biliary colics (≥ 0.5 hour) in 22 patients undergoing ESWL and 22 undergoing conventional cholecystectomy [analysis per protocol]. In both treatment groups, all patients experienced at least one biliary colic before therapy.

Period (months)	E-group (n)			Y-C p-value	C-group (n)		
	0x	≥1x	total		0x	≥1x	total
0-3	10	12	22	<0.01*	20	2	22
3-6	20	2	22	NS	21	1	22
6-12	20	1	21	NS	20	2	22
12-18	18	0	18	NS	16	2	18
	X^2 for trend: p<0.001				X^2 for trend: NS		

E-group = ESWL-group; C-group = cholecystectomy-group; Y-C = Yates-Cochran test between groups [E vs. C] at certain periods; NS = not significant ; *) p<0.05 if adjusted according to Bonferroni

Trend analyses showed that both fatty food upset and stomach swelling improved significantly in the C-group, while nausea improved significantly in the E-group. Between the E- and C-group there was only at one occasion a significant difference in reported frequency: for fatty food upset at 18 months ($p<0.05$), in favour of cholecystectomy. For vomiting, pyrosis, belching, constipation and diarrhea, no differences were found in reported frequencies between before and 3, 6, 12, 18 months after therapy. Nor were there any significant differences between the E- and C-group at any time. Analysis of the total number of moderate or severe complaints per patient showed also no difference between the two groups.

Gastrointestinal complaints and stone clearance

There was no relationship between stone clearance and gastrointestinal symptoms in the E-group at 12 months after therapy.

Stone clearance and background variables

In the E-group, there was no significant difference between the frequency of patients eventually becoming free of concrements on one hand and sex, number of stones (1 vs. >1), diameter of stones (≤15mm vs. >15mm), stone calcifications (none vs. ≤ 2mm), age (≤50 vs. >50 yrs) and body mass index (≤25 vs. >25) before therapy on the other hand.

Table 3: Comparison in reported frequencies (in %) of fatty food upset, nausea and stomach swelling between patients randomized to ESWL and cholecystectomy [intention-to-treat analysis].

time (months)	fatty food upset			nausea			stomach swelling		
	E	**C**	**E/C**	**E**	**C**	**E/C**	**E**	**C**	**E/C**
0	35	44	NS	30	33	NS	35	48	NS
3	33	21	NS	19	13	NS	29	29	NS
6	15	29	NS	0	13	NS	20	13	NS
12	26	13	NS	10	26	NS	11	10	NS
18	22	0	<0.05	0	6	NS	28	18	NS
X^2 for trend:	NS	<0.01		<0.01	NS		NS	<0.02	

E = ESWL (extracorporeal shock wave lithotripsy)

C = conventional cholecystectomy

E/C = Chi-square test between therapies

NS = not significant

Discussion

Many reports have already been published on biliary and gastrointestinal symptoms in relation to gallstones and gallstone therapy. Most studies, however, are retrospective [5-7], while others are prospective but not controlled [8,9]. Usually they do not compare different treatment modalities [6-11] and sometimes include emergency surgery [7,12], common bile duct explorations [6,7,12] and procedures concomitant to cholecystectomy [6]. Reports on symptomatology after ESWL are scarse and usually report exclusively on patients who became free of stones, which is only the minority of treated patients [9]. These different designs make comparison difficult. Our study was performed to overcome these methodologic problems and it is therefore regrettable that the number of patients is limited. The limited

patient entry was caused by several factors. At first, eligibility for ESWL (and thus for the study) was limited [13]. Also many patients had a specific preference for one of the treatment arms, hampering randomization: outside the context of our trial, another 90 patients, who refused randomization, were treated with ESWL. Especially preference for laparoscopic cholecystectomy, which was introduced during our study, impaired randomization almost completely (unpublished observations). Still, follow-up of this study is adequate, so conclusions may be drawn from the results. Furthermore, another 23 patients were followed in addition by the same protocol without being randomized. Their results were equal to those of the randomized patients (not shown), making the effect estimates even more precise.

Our study demonstrated that biliary colics respond to both ESWL and cholecystectomy. Since both treatment modalities are relatively safe, we confirmed that treating symptomatic gallstone patients is highly justifiable [7,8]. Cholecystectomy, however, cures biliary colics more consistently and some 3 months earlier than ESWL, making it superior to ESWL.

We also found that fatty food upset and stomach swelling responded to cholecystectomy. Nausea improved after ESWL. These responses take, however, at least 6 months. Furthermore, 5 other gastrointestinal symptoms did not respond to either form of treatment. Finally, we found in the E-group that whether a patient was free of concrements or not, did not influence the frequency of reported gastrointestinal symptoms. However, it cannot be excluded that the results of this subgroup analysis may be subject to a type II-error, because of the limited number of patients. Still, our findings support the notion that gastrointestinal symptoms are most probably not related to the presence or absence of gallstones and, therefore, should not be used as an indication for elective gallstone therapy [4,11,14-17].

To our knowledge, there is only one report that investigated symptomatolgy after ESWL and conventional cholecystectomy in a randomized way as we did, although the objective of that particular study was a cost-effectiveness analysis [18]. Also in this series, only patients with uncomplicated symptomatic gallstones were studied. However, on other points, our study differed from that of the Sheffield-group. Our lenght of follow-up, stone clearance rate and complication rates compare favourably. Moreover, we used a different kind of lithotriptor and performed ESWL solely on an outpatient basis. Also, we did not have a subgroup of patients treated with lithotripsy alone, but treated all patients adjuvantly with OBA after ESWL, which is superior to ESWL alone [19]. Finally, we did not treat heavily calcified stones.

Despite these apparent differences, our findings are surprisingly concordant. Also in the report of the Sheffield-group, a significant difference in pain experience post-treatment could be demonstrated in favour of cholecystectomy. Also, no consistent patterns of differences between cholecystectomy and lithotripsy could be demonstrated in gastrointestinal symptoms: if differences were observed, they were usually small and there was some evidence that cholecystectomy produced a greater reduction in a small subset of gastrointestinal symptoms than ESWL. Finally, also here, stone clearance was not related to self-reported gastrointestinal symptoms.

The results of a randomized study comparing ESWL with laparoscopic cholecystectomy were published only recently [20]. The studied population is remarkably identical to ours regarding age and sex and in this trial, colics recurred in 57% of the patients after ESWL. The authors stress that in 26% of these patients, colic caused a day away from usual activities. Like us, they also demonstrated that cholecystectomized patients may suffer from biliary colics. It should be noted, however, that this occurs in only the minority of patients (2/25). Finally, it is noteworthy that also here, a considerable number of patients crossed over from one treatment group to the other.

Our treatment protocol differed from most ESWL protocols regarding the start of OBA administration. Where we started OBA therapy after the first ESWL session, most protocols began two weeks prior to ESWL in order to achieve cholesterol desaturation prior to lithotripsy [1,2,18]. However, because OBA therapy is accompanied by a prolonged gallbladder emptying [21,22], we considered it theoretically more advantageous to start with OBA later. In this way, the gallbladder would have the opportunity to clear most (or at least some) of the smaller fragments that occur after lithotripsy, by natural expulsion [9]. The disadvantage of reaching cholesterol desaturation two weeks later in other protocols, was considered to be of little importance since OBA therapy has usually to be maintained for 6-12 months.

Our overall stone clearance rate is relatively low compared to other reports [2]. This is most probably due to the fact that we treated up to 10 stones, where others usually treat not more than three stones [2]. We discussed this finding already in a previous report on 83 patients treated with ESWL [23]. In fact, we now recommend to treat only radiolucent, solitary stones because of the poor clearance rates for multiple stones [24].

Considering our results and the fact that cholecystectomy is not accompanied with

gallstone recurrence, we conclude that cholecystectomy is to be preferred to ESWL. Our finding that also ESWL can be accompanied by severe complications and that nearly a quarter of the patients eventually undergo cholecystectomy support this conclusion. However, as long as patients satisfy strict entry criteria, there should be no objection against patients' preference for ESWL, although it is not as cost-effective as cholecystectomy [18,25-27]. In patients with an increased operative risk, ESWL may still offer a solution.

References

1. 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.
2. Barkun ANG, Ponchon TP. Extracorporeal biliary lithotrips: review of experimental studies and clinical update. Ann Intern Med 1990;112:126-37.
3. McSherry CK. Cholecystectomy : the gold standard. Am J Surg 1989;158:174-8.
4. 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.
5. Stefanini P, Carboni M, Patrassi N, et al. Factors influencing the long term results of cholecystectomy. Surg Gynecol Obstet 1974;139:734-8.
6. Gilliland TM, Traverso LW. Modern standards for comparison with alternative treatments for symptomatic cholelithiasis with emphasis on long term relief of symptoms. Surg Gynecol Obstet 1990;170:39-44.
7. Konsten J, Gouma DJ, Meyenfeldt MF von, et al. Long-term follow-up after open cholecystectomy. Br J Surg 1993;80:100-2.
8. Ros E, Zambon D. Postcholecystectomy symptoms: a prospective study of gall stone patients before and two years after surgery. Gut 1987;28:1500-4.
9. Lee SH, Burhenne HJ. Persistence of symptoms after gall bladder clearance with cholecystolithotripsy. Gut 1991;32:536-8.
10. Gunn A, Keddie N. Some clinical observations on patients with gallstones. Lancet 1972;ii:239-41.
11. Wegge C, Kjaergaard J. Evaluation of symptoms and signs of gallstone disease in patients admitted with upper abdominal pain. Scand J Gastroenterol 1985;20:933-6.
12. Bates T, Ebbs SR, Harrison M, et al. Influence of cholecystectomy on symptoms. Br J Surg 1991;78:964-7.
13. Plaisier PW, Hul RL van der, Nijs HGT, et al. Eligibility for extracorporeal shock wave lithotripsy of gallbladder stones using different entry criteria. J Stone Dis 1993;5:101-6.
14. Price WH. Gall-bladder dyspepsia. Br Med J 1963;ii:138-41.
15. Koch JP, Donaldson RM. A survey of food intolerances in hospitalized patients. N Engl J Med 1964;271:657-60.
16. Wegge C, Kjaergaard J. Evaluation of symptoms and signs of gallstone disease in patients admitted with upper abdominal pain. Scand J Gastroenterol 1985;20:933-6.
17. Paumgartner G, Carr-Locke DL, Roda E, et al. Biliary stones: non-surgical therapeutic approach. Gastroenterol Int 1988;1:17-24.
18. Diehl AK, Sugarek NJ, Todd KH. Clinical evaluation for gallstone disease: Usefulness of symptoms and signs in diagnosis. Am J Med 1990;89:29-33.
19. Nicholl JP, Brazier JE, Milner PC, et al. Randomised controlled trial of cost-effectiveness of lithotripsy and open cholecystectomy as treatments for gallbladder stones. Lancet 1992;340:801-7.
20. Schoenfield LJ, Berci G, Carnovale RL, et al. The effect of ursodiol on the efficacy and safety of extracorporeal shock-wave lithotripsy of gallstones: the Dornier National Biliary Lithotripsy Study. N Engl J Med 1990;323:1239-45.
21. Barkun AN, Barkun JS, Sampalis JS, et al. A randomized clinical trial comparing gallbladder stone shock

wave lithotripsy to laparoscopic cholecystectomy. Gastroenterology 1993;104:A2.
22. Forgacs IC, Maisey MN, Murphy GM, et al. Influence of gallstones and ursodeoxycholic acid on gallbladder emptying. Gastroenterology 1984;87:299-307.
23. Festi D, Frabboni R, Bazzoli F, et al. Gallbladder motility in cholesterol gallstone disease: effects of ursodeoxycholic acid administration and gallstone dissolution. Gastroenterology 1990;99:1779-85.
24. Toom R den, Vergunst H, Nijs HGT, et al. Electromagnetic shock wave lithotripsy of gallbladder stones: a wide range of inclusion criteria. Am J Gastroenterol 1992;87:498-503.
25. Plaisier PW, Hul RL van der, Toom R den, et al. Gallstone lithotripsy: the Rotterdam experience. Hepatogastroenterol (in press).
26. Rothschild JG, Holbrook RF, Reinhold RB. Gallstone lithotripsy versus cholecystectomy: a preliminary cost-benefit analysis. Arch Surg 1990;125:710-4
27. Bass EB, Steinberg EP, Pitt HA, et al. Cost-effectiveness of extracorporeal shock-wave lithotripsy versus cholecystectomy for symptomatic gallstones. Gastroenterology 1991;101:189-99.
28. Nealon WH, Urrutia F, Fleming D, et al. The economic burden of gallstone lithotripsy: will cost determine its fate? Ann Surg 1991;213:645-50.

Quality of life after gallstone therapy: results of a randomized study comparing lithotripsy with open cholecystectomy

P.W. Plaisier, R.L. van der Hul, H.G.T. Nijs, R. den Toom, O.T. Terpstra, H.A. Bruining

Eur J Surg (accepted for publication)

Abstract

A randomized study was conducted in order to compare quality of life after extracorporeal shock wave lithotripsy (ESWL) and open cholecystectomy, the gold standard. In the period October 1989 - March 1992, 23 patients were randomized to ESWL and 26 to open cholecystectomy. Health questionnaires were filled out before and at 3, 6 and 12 months after therapy. Median follow-up was 18 months. Both treatment modalities improved quality of life. Open cholecystectomy improved quality of life significantly better than ESWL during the course of one year. It is concluded that open cholecystectomy is superior to ESWL in improving quality of life. Therefore, cholecystectomy remains the therapy of choice for symptomatic gallstones. However, in patients who are unfit or unwilling to undergo surgery, ESWL is an adequate form of treatment because the majority of patients tend to benefit from it in terms of quality of life.

Introduction

When extracorporeal shock wave lithotripsy (ESWL) was introduced as a promising alternative to cholecystectomy, it was obvious that it was not suitable to treat all stones. It also harboured the potential risk of stone recurrence. Considering this theoretical disadvantage of ESWL, the outcome of an evaluation of ESWL should be measured in other terms than merely in terms of stone clearance. Ideally, such a study should be conducted as a randomized trial, comparing ESWL with open cholecystectomy, the gold standard [1,2]. We conducted such a trial to detect any differences in terms of quality of life between ESWL and conventional cholecystectomy. For the methods and results of ESWL and cholecystectomy is referred to Chapter 5 of this thesis.

Patients and methods

From October 1989 - March 1992, 49 patients were randomized, 23 for ESWL (E-group) and 26 for cholecystectomy (C-group). Randomization was performed by computer after stratification for number of gallstones (1, 2-5, 6-10 stones). Patients were recruited from a so-called 'gallstone clinic', a surgical outpatient clinic, solely for gallstone patients. Inclusion and exclusion criteria for the study were the same as the entry criteria for ESWL, as depicted in Chapter 4 (Table 1). Patients were diagnosed as 'symptomatic' gallstone patients when they met the GREPCO-definition [3]. After a 6 month-intake period, in which no patient consented in randomization, patient intake was stopped in March 1992.

Follow-up

Follow-up consisted of self-administered health profile questionnaires, taken before therapy (t=0) and at 3, 6 and 12 months after therapy. A validated, translated version of the Nottingham Health Profile (NHP) was used [4]. The NHP is a questionnaire which assesses 6 aspects of quality of life (so-called 'dimensions'), being: physical mobility, pain, sleep, energy, social and emotional reactions function. Each domain of these dimensions contains items of questions requiring a 'yes' or 'no' answer (dichotomous). If all questions are answered 'yes', the patient scores highest, but is considered having the least quality of life. A weighting system is derived from extensive validation excercises, so that a positive response for each item is multiplied by a factor before aggregation. Hence, besides the summing up of the scores for individual items, also weighted scores can be calculated taking

the individual weight of each question and/or each dimension into account. 'Health gain' can than be defined as the decrease in median score (ergo: the median decrease in positively answered questions). NHP's were sent by mail and double-checked 1 month after receipt. Double-checking was performed by interviews, taken at the outpatient clinic (E-group) and by phone (C-group).

Statistics

Statistical analysis was done with the non-parametric Friedman's analysis of variance and the Chi-square test for comparing proportions. Analyses were performed on an intention-to-treat basis.

Results

Characteristics of the randomized patients were already depicted in Chapter 5 (Table 1). Mean follow-up was 19.0 months (median : 18.0; range : 12-24). There were no differences between the two groups at baseline. No patient was lost to follow-up.

Quality of life

NHP-questionnaires were returned and filled out correctly in 96% of the cases. So, from 23 E-group and 24 C-group patients, data were available before and 3, 6, 12 months after therapy. There were no significant differences between intention-to-treat analyses and analyses per protocol.

It was found that the median overall percentage of items answered positively, decreased in both treatment groups after therapy (Figure 1). However, these decreases were more profound and significant for the C-group during the course of 1 year ($p < 0.01$) compared to the E-group (Table 1). Table 1 also shows that the decrease in median percentage of positively answered questions is mainly accounted for by the questions from the pain, energy and emotional reaction dimensions. Of these three, only the pain and the emotional reaction dimension were statistically significant ($p < 0.05$). Health gain was also found in the C-group after scores weighted for items alone and items and dimensions (both: $p < 0.01$). Health gains in the E-group for both weighted calculations were not statistically significant.

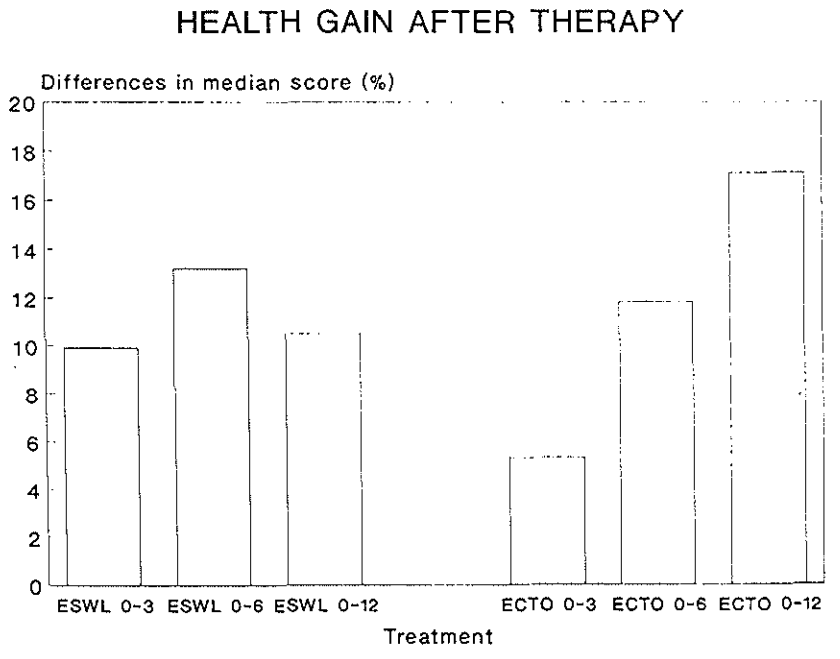

Figure 1: Median total scores (in %) on Nottingham Health Profiles; on the abcissa: months

ESWL : extracorporeal shock wave lithotripsy

ECTO : cholecystectomy

Table 1: health gain (in %) at 12 months after therapy (defined as the difference in median scores on the quality of life questionnaires compared to the situation before therapy), divided into the different dimensions; analsis via intention-to-treat; underlined are statistically significant p-values

	E-group (n=23)		C-group (n=24)	
Dimension	Health gain in 1 year	Friedman's test: p-value	Health gain in 1 year	Friedman's test: p-value
energy	0.0	0.503	26.0	0.065
pain	5.8	0.319	12.9	0.034
emotions	7.2	0.281	17.0	0.035
sleep	12.5	0.440	12.6	0.284
social	0.0	0.742	0.0	0.853
mobility	0.0	0.849	11.2	0.565
total	10.5	0.113	17.1	0.003

E-group : extracorporeal shock wave lithotripsy-group

C-group : cholecystectomy-group

Discussion

Open cholecystectomy has been the standard operation for gallstone disease for over a century. It has tremendous clinical and economical consequences: e.g. in the United Kingdom and Ireland to 50,000 cholecystectomies are performed each year [5]. Since cholecystectomy is accompanied by a certain morbidity [1], ESWL was introduced as an alternative to cholecystectomy with very promising results in a series of 175 patients [6].

Both cholecystectomy and ESWL are accompanied by low mortality rates. Therefore, using mortality rates to detect any difference between the two treatment arms is insensitive and thus inappropriate [7-9]. Especially, minimally invasive surgery is an area well suited for quality-of-life research [9]. So, when we started our study, health status-analysis was considered a good method since especially in the treatment of symptomatic gallstones, improving the patient's quality of life is always be the most important aim of intervention [10]. In fact, any form of elective surgery is directed primarily to improvement of quality of life, i.e. the relief of disability, discomfort and disfigurement [7,11].

We chose the Nottingham Health Profile, since it is well validated and one of the most widely used general measures of quality of life [8]. Moreover, it has shown reliable in a large number of different fields of medicine and surgery, can be easily administered by mail and makes relatively small demands on patient time and effort [8,9,12]. Health questionnaires not only enabled us to assess the outcome of gallstone therapy but also enabled us to compare different treatment modalities.

We found that both ESWL and cholecystectomy improved quality of life, when measured with the NHP and justified the treatment of symptomatic gallstone patients. However, in the C-group the health gain was significantly better. This improvement was found in weighted and unweighted NHP-scores and mainly in the pain and emotional reactions dimension. The influence of the two treatment modalities on quality of life is identical to the influence on symptomatology. Also specific gallstone symptoms respond to both treatment modalities and this response is more pronounced after cholecystectomy than after ESWL [13,14]. Based on these data, the fact that ESWL only clears stones partially and because ESWL is accompanied by the possibility of stone recurrence, open cholecystectomy is superior to ESWL. Our finding that still nearly a quarter of the patients eventually undergo cholecystectomy, finally, supports this conclusion.

To our knowledge, there is only one report that investigated quality of life after ESWL

and cholecystectomy, although the main objective of this report was a cost-effectiveness analysis [13]. In this report both therapies improved quality of life significantly in most NHP dimensions, while there were no differences in median health status in the two groups in any dimension at 12 months. A possible explanation of the fact that we did not find any statistically significant differences in health gains in patients treated with ESWL, is that we did not have a sub-group of patients nót adjuvantly treated with bile acids. We also used another type of lithotriptor.

We found that conventional cholecystectomy is superior to ESWL in terms of quality of life improvement. Only recently, a large panel of specialists from different disciplines declared that open cholecystectomy should still be judged the gold standard [2]. In current medical practice, however, both treatment modalities have been surpassed bij laparoscopic cholecystectomy [15], although it must be noted that this new procedure has not been properly assessed in a randomized trial [9,16]. Obviously, this development hampered patient accrual in our study. Only about a third of the originally planned n.mber of patients could be recruited and a subanalysis on initial stone load could not be performed due to the fact that the subgroups included too few patients.

The general adoption of laparoscopic cholecystectomy probably leaves one of the most important conclusions of our study that the NHP is a useful tool for research in general surgery, even if numbers of patients are relatively small. In cases where laparoscopic cholecystectomy is not feasible, e.g. after previous upper abdominal surgery, open cholecystectomy is to be preferred to ESWL. However, in patients who are unfit or unwilling to undergo surgery, ESWL is an adequate form treatment because the majority of patients obviously benefit from it in terms of quality of life.

References

1. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989; 158:174-8.
2. Soper NJ, Dunnegan DL. Summary of NIH consensus development conference "Gallstones and laparoscopic cholecystectomy". World J Surg 1993;17:21.
3. 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.
4. Hunt SM, McEwen J, McKenna SP. Measuring health status. London: Croom Helm, 1986.
5. Walsh TN, Russell RCG. Cholecystectomy and gallbladder conservation. Br J Surg 1992;79:4-5.
6. 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.

7. Bunker JP, Wennberg JE. Operation rates, mortality statistics and the quality of life. N Engl J Med 1973;289:1249-51.
8. O'Boyle CA. Assessment of quality of life in surgery. Br J Surg 1992;79:395-8.
9. Fraser SCA. Quality-of-life measurement in surgical practice. Br J Surg 1993;80:163-9.
10. Eypasch E. Troidl H, Wood-Dauphinée S, et al. Quality of life and gastro-intestinal surgery: a clinimetric approach to developing an instrument for its measurement. Theor Surg 1990;5:3-10.
11. Goligher JC. Judging the quality of life after surgical operations. J Chron Dis 1987;40:631-3.
12. O'Brien BJ, Buxton MJ, Ferguson BA. Effectiveness of heart transplant programmes: quality of life data and their relationship to survival analysis. J Chron Dis 1987;40(suppl1):137S-53S.
13. Nicholl JP, Brazier JE, Milner PC, et al. Randomised controlled trial of cost-effectiveness of lithotripsy and open cholecystectomy as treatments for gallbladder stones. Lancet 1992;340:801-7.
14. Plaisier PW, Hul RL van der, Nijs HGT, et al. The course of biliary and gastro-intestinal symptoms after gallstone therapy: results of a randomised study comparing extracorporeal shock wave lithotripsy with cholecystectomy. Am J Gastroenterol (in press).
15. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991;324:1073-8.
16. Neugebauer E, Troidl H, Spangenberger W, et al. Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. Br J Surg 1991;78:150-4.

Cost-effectiveness of extracorporeal shock wave lithotripsy and cholecystectomy

P.W. Plaisier, B.A. van Hout, H.G.T. Nijs

Abstract

The possible acceptance of extracorporeal shock wave lithotripsy (ESWL) as a serious treatment modality for symptomatic gallstones would not only have depended on its outcomes, but also on the accompanying costs. In this chapter, the results of several studies on the cost-effectiveness of ESWL are discussed. It is concluded that ESWL is not as cost-effective as cholecystectomy. From an economic point of view, it is, therefore, unlikely that ESWL emerges as the treatment of choice for symptomatic gallstones. ESWL may only play a role for elderly individuals with solitary stones.

Introduction

Evaluating the economic impact of medical procedures is of increasing importance in Western societies. This is especially true in the case of new technologies. Nowadays, the acceptance of any new treatment modality depends not only on its outcomes, but also on the accompanying costs.

When the Rotterdam Gallstone (ROGAL) Study was started, a cost-effectiveness-analysis (CEA) was included. The results of this adjoined study are described in detail elsewhere [1]. In this chapter, the available reports regarding the cost-effectiveness of extracorporeal shock wave lithotripsy (ESWL) will be discussed.

Results from the ROGAL Study

The CEA of the ROGAL Study was performed by the Institute for Medical Technology Assessment under the supervision of the Dutch National Health Insurance Council. In 1992, this council decided to stop financial support. First, because patient accrual was poor (Chapter 9). And second, because the determination of the economic value of ESWL had lost its relevanance after the universal adoption of laparoscopic cholecystectomy. The CEA was, therefore, stopped and a comparison of costs and effects was based on the then available data.

costs

Costs calculations were based on the data, collected in the period September 1989 - January 1992. The data included 42 patients with a follow-up of 3-27 months.

It was estimated that the mean factual costs for patients receiving ESWL were *f*3676 (Table 1). A breakdown of the costs shows the relative importance of the costs of the interventions. Of these, the costs of the ESWL procedures are highest (78%). Although an ESWL session costed only *f*1259, patients required an average of 2.13 sessions, resulting in *f*2681 per ESWL patient. The costs of pre- and posttreatment follow-up were primarily due to the regular ultrasonographic examinations (*f*648). Additional costs consisted of adjuvant bile acid therapy and hospitalization. Bile acid therapy costed *f*5.43 per day and were taken for an average duration of 1 year. The costs of hospitalization were caused by the fact that some patients eventually require cholecystectomy, although these costs did not have a substantial impact because the mean hospitalization time of ESWL patients was only

1.6 days.

Table 1: mean costs per patient for extracorporeal shock wave lithotripsy (ESWL) and cholecystectomy (in Dutch guilders); in parentheses: costs as a percentage of the total

	ESWL		Cholecystectomy	
Laboratory tests	139	(4)	216	(14)
Radiological examinations	679	(18)	45	(3)
Interventions	2858[1]	(78)	1333[2]	(84)
Total	3676		1594	

1) including ESWL, electrocardiography, cholecystectomy and endoscopic retrograde cholangio-pancreatricography.
2) including cholecystectomy and electrocardiography.

The total mean costs (i.e. the mean factual costs and the mean additional costs) for ESWL were eventually estimated at *f*6700 (Figure 1). It should be noted, however, that this estimate did not include costs induced by eventual stone recurrence. This had not been observed. A more substantial follow-up, however, showed stone recurrence in 14% of the ESWL patients (Chapter 5).

Mean factual costs per cholecystectomy patient were *f*1594 (Table 1). These costs were covered almost exclusively by the interventions. When the costs for hospitalization were added, the mean total costs for cholecystectomy was *f*4650 (Figure 1). There was no significant difference between the median hospitalization time of patients undergoing cholecystectomy in or outside the trial. This was checked in a series of all patients undergoing cholecystectomy (n=170) at the University Hospital 'Dijkzigt' in 1990.

When comparing the course of the cumulated costs during treatment, there was a marked difference between the two treatment arms. The mean total costs of cholecystectomy were reached within two weeks, whereas the costs of ESWL rose steadily during the entire follow-up (Figure 1). Indirect costs, such as those related to absence from work, were not calculated due.

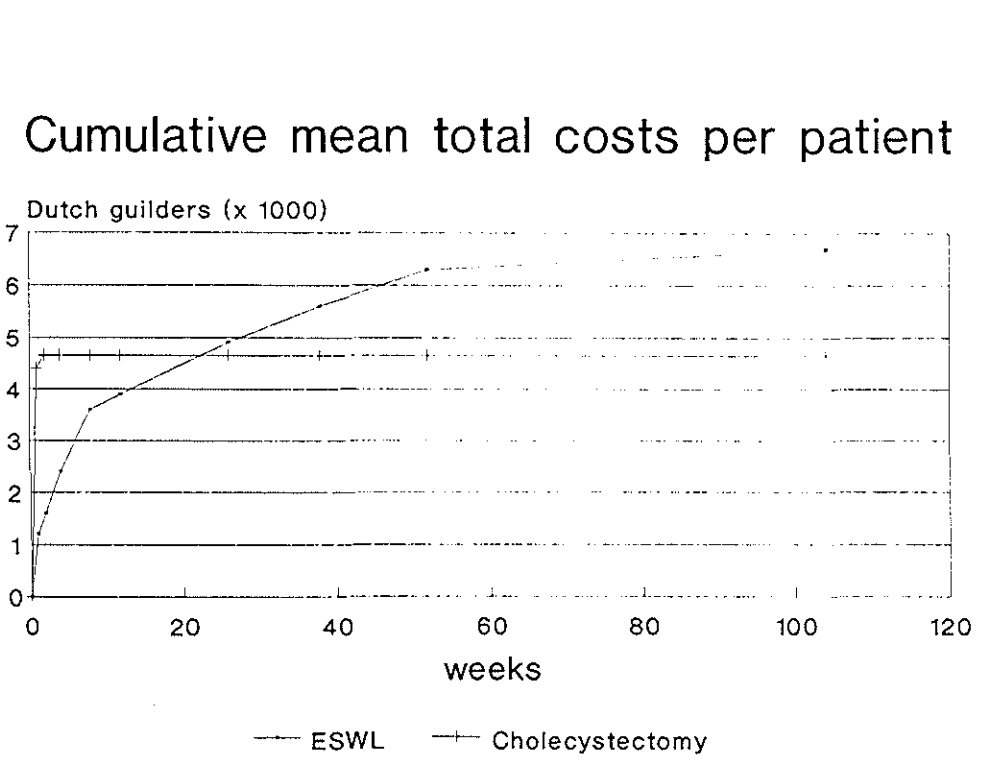

Figure 1: cumulative costs per patient for extracorporeal shock wave lithotripsy (ESWL) and cholecystectomy

In conclusion, ESWL is substantially more expensive than cholecystectomy in terms of direct medical costs. A major reduction in costs may be achieved if the average number of ESWL sessions can be reduced or if ESWL would be effective without adjuvant treatment with bile acids.

effects

For a detailed analysis of the effects of ESWL and cholecystectomy, the reader is referred to the Chapters 5 and 6 of this thesis.

cost-effectiveness

Considering that ESWL is more expensive in direct medical costs and has less pronounced effects than cholecystectomy, it is concluded that ESWL is not as cost-effective as cholecystectomy.

Discussion

The first publications on the costs of ESWL calculated only in-hospital costs of ESWL in regard to cholecystectomy [2-4]. Actual CEA's of ESWL appeared later [5,6]. Reports were based on either computer models [5,6] or prospective findings [4,7].

Already the first study revealed that ESWL was accompanied by higher mean costs than cholecystectomy ($8100 vs. $6240) [2]. This conclusion was later confirmed by other studies [3-5,7], in which varied subsets of costs (e.g. for laboratory tests and professional) were used and ESWL was perfomed either as an outpatient [1,3,5] or an inpatient [2,4,7] procedure.

Nealon and co-workers found approximately the same mean calculated costs for the ESWL-procedure as Rothschild ($8275) [3]. When the costs for bile acid therapy, screening and follow-up were added, the total costs were calculated as being $12,186. When patients who finally required cholecystectomy or in whom lithotripsy failed were excluded from the denominator, the total costs of ESWL were eventually $15,087.

A multispecialty panel from the John Hopkins University also found that the costs of ESWL outranged those of cholecystectomy [5]. Survival and quality-adjusted survival was better for ESWL than cholecystectomy, but this is rather obvious considering the marked difference in mortality. A subanalysis showed that ESWL became 10-20 times as cost-effective in elderly patients.

Also in the study of The Sheffield Group, the overall mean costs per patient of cholecystectomy were significantly less than for ESWL [7]. This was, however, more pronounced for large stone loads than small stone loads [7]. This result was also found in other studies [5,8].

There is only one report that concluded that ESWL should be the procedure of choice from society's point of view [6]. Still, a major drawback of this study was that calculations were based on the stone clearance and complication rates, as published by the Munich Group [9]. Considering that these data have never been reproduced [3,10], the calculations may be regarded as too optimistic and clearly prepossessing ESWL. Another drawback was that it was assumed that common bile duct explorations occurred 25% of the cholecystectomies. This percentage seems rather high and clearly disadvantages cholecystectomy for it has been shown that the complication and death rates of a cholecystectomy largely depend on whether it is accompanied by a common bile duct exploration [11]. A final drawback was that only calculations were made for patients under the age of 65 with solitary stones with a diameter

of ≤20 mm. It has been shown that these patients represent only about 10% of the gallstone patient population [12].

In conclusion, all major reports agree that ESWL is accompanied by more costs than cholecystectomy. Most actual CEA's conclude that ESWL is, furthermore, less effective. Moreover it is likely that the one study that suggested that ESWL would be more cost-effective, made the wrong assumptions.

From an economic point of view, it is unlikely that ESWL will emerge as the treatment of choice for symptomatic gallstones. Preliminary cost-utility analyses on laparoscopic cholecystectomy indicate that it is even less expensive and more effective than open cholecystectomy [8,13,14]. ESWL may, therefore, only play a role for elderly individuals with solitary stones.

References

1. Seerden R, Ineveld BM van, Nijs HGT, et al. Kosten-effectiviteits-analyse van E.S.W.L. versus Cholecystectomie. Rapport 93.22. Instituut Medical Technology Assessment, Erasmus Universiteit Rotterdam, Rotterdam, 1993.
2. Rothschild JG, Holbrook RF, Reinhold RB. Gallstone lithotripsy versus cholecystectomy: a preliminary cost-benefit analysis. Arch Surg 1990;125:710-4.
3. Nealon WH, Urrutia F, Fleming D, et al. The economic burden of gallstone lithotripsy: will cost determine its fate? Ann Surg 1991;213:645-50.
4. Deleu HWO, Jansen FMBH, Stevering CJT. Schokgolflithotripsie: verguizen of vergruizen? -de galblaassteenvergruizer nader bekeken. Med Contact 1991;46:943-7.
5. Bass EB, Steinberg EP, Pitt HA, et al. Cost-effectiveness of extracorporeal shock-wave lithotripsy versus cholecystectomy for symptomatic gallstones. Gastroenterology 1991;101:189-99.
6. Stengele U, Baumgartner BR, Chezmar JL, et al. Biliary lithotripsy versus cholecystectomy: a cost utility analysis. J Lithotripsy & Stone Dis 1991;3:133-40.
7. Nicholl JP, Brazier JE, Milner PC, et al. Randomised controlled trial of cost-effectiveness of lithotripsy and open cholecystectomy as treatments for gallbladder stones. Lancet 1992;340:801-7.
8. Elewaut A, Crape A, Afschrift M, et al. Results of extracorporeal shock wave lithotripsy of gall bladder stones in 693 patients: a plea for restriction to solitary radiolucent stones. Gut 1993;34:274-8.
9. 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.
10. Plaisier PW, Hul RL van der, Terpstra OT, et al. The current role of extracorporeal shock wave therapy in surgery. Br J Surg (in press).
11. McSherry CK, Glenn F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. Ann Surg 1980;191:271-5.
12. Plaisier PW, Hul RI van der, Nijs HGT, et al. Eligibility for extracorporeal shock wave lithotripsy of gallbladder stones using different entry criteria. J Stone Dis 1993;5:125-30.
13. Bass EB, Pitt HA, Lillemoe KD. Cost-effectiveness of laparoscopic cholecystectomy versus open cholecystectomy. Am J Surg 1993;165:466-71.
15. Voyles CR. The laparoscopic buck stops here! Am J Surg 1993;165:472-3.

Radiographic features of oral cholecystograms of 448 symptomatic gallstone patients: implications for nonsurgical therapy

P.W. Plaisier, K. Brakel, R.L. van der Hul, H.A. Bruining

Eur J Radiol (in press)

Abstract

Because radiographic findings at oral cholecystography (OCG) have implications for the eligibility for nonsurgical therapy of elderly patients, we investigated the OCGs of 448 symptomatic gallstone patients (109 male, 339 female; mean age 49.8 $\pm$ 14 [range: 21-88]). Opacification of the gallbladder was found in 323 cases (72.1%). Calcifications of gallstones were found in 85 opacified gallbladders (26.3%). Solitary and multiple stones were calcified in 35.3% and 18.2%, respectively [$p < 0.0005$]. When divided into two groups (≤ 40 years and > 40 years), there was a significant increase in calcifications [$p < 0.02$] and a non-significant increase in opacification with increasing age. It is concluded that age is a determinant for calcification of gallstones and not for opacification of the gallbladder. Because multiple stones are proportionately observed more in clinical studies than in epidemiologic studies, it is suggested that multiplicity of stones predisposes to biliary complaints. That solitary stones are more likely to be calcified than multiple stones, adds to the hypothesis that solitary and multiple stones have a different pathogenesis. Elderly patients, in whom nonsurgical therapy is most likely to be indicated and cost-effective, are less likely to be suitable for this form of treatment, because age is a determinant for stone calcification.

Introduction

The development of oral cholecystography (OCG) is one of the milestones in the history of roentgenology [1]. It has been the unchallenged standard in the diagnosis of gallbladder disease for half a century, but less than five years after the introduction of ultrasonography (US), OCG disappeared almost entirely from clinical practice. The introduction of several nonsurgical treatment modalities for gallstone disease [2-8], resurrected the use of OCG for it can provide information on stone composition and patency of the cystic duct.

We analyzed the OCGs of 448 symptomatic gallstone patients for their radiographic features. The aim of this study was twofold. First, we wanted to investigate if age is a determinant of calcification of gallstones and nonopacification of the gallbladder, because this would have implications for the eligibility for nonsurgical therapy of elderly patients. Second, we wanted to investigate to what extent our clinical findings agreed with epidemiologic findings. This paper reports our findings.

Patients and methods

In 1988 a surgical outpatient biliary clinic was started. It was especially designed to select patients for alternative treatment modalities for gallstone disease, such as orally administered bile acids [2,3], contact dissolution [4,5], extracorporeal shock wave lithotripsy (ESWL) [6,7] and rotary contact lithotripsy [8].

In the period April 1988 - April 1992, 774 patients visited this clinic. All patients were analyzed according to protocol: patient's history, physical examination and -if patients were considered symptomatic- laboratory tests and radiologic examination. Patients were considered symptomatic only, if they had experienced one or more episodes of abdominal pain (usually epigastric or right upper quadrant) lasting more than 15 min but less than 5 h, according to the Roma Working Team definition [9].

Radiologic examination consisted of US and OCG. Calcifications were only recorded in visualized gallbladders, analogously to the GREPCO- study [10]. Results of recent examinations done elsewhere, were not repeated and used in this study. An OCG was not performed, when the patient refused a nonsurgical therapeutic option or if previous US examination excluded the patient by our ESWL entry criteria (>10 stones, stones with a diameter <5mm, common bile duct stones, aneurysms or cysts in the shock wave path and pregnancy) [7].

One-hundred and thirteen patients (14.6%) were excluded from OCG, because they had no biliary symptoms. Of the 661 symptomatic patients, 213 patients (32.2%) had no OCG performed because they preferred cholecystectomy. OCG was performed after intake of iocematic acid (Cholebrine®) the evening before the examination. Intake of Cholebrine® [iocematic acid] was according to body weight: <60kg : 3.00g [1.86g]; 60-90kg : 4.50g [2.79g]; >90kg : 6.00g [3.72g]. Cholebrine® was taken orally in two steps with an interval of one hour, with some water, after which the patient was not allowed to eat, drink or smoke. Intake was planned in such a way, that fasting time was approximately 12 h.

Due to logistical reasons we were not able to provide repeat doses in the case of nonvisualization of the gallbladder. However, it has been demonstrated that in patients in whom normal opacification occurs after a repeat dose, the initial dose already gave a faint visualization of the gallbladder [11]. Therefore, we categorized faint visualization as opacification being present.

All data were recorded on standardized forms by the performing radiologists, without knowledge of previous examinations. On these standardized forms used for OCG the radiologist recorded whether there was opacification (yes/no), the number of gallstones (0, 1, 2, 3, 4, 5, 6-10, >10), the diameter of the largest stone (in mm), whether the stones were calcificied (yes/no) and if there was buoyancy [the presence of floating stones] (yes/no). In addition, if present, the sort of calcification (core, rim<2mm, rim>2mm, total) was recorded. Finally, in the case the gallbladder did not opacificy, whether there was contrast in the small bowels (yes/no) to determine the patient's compliance. In the case of nonspherical stones the largest diameter was recorded. Measurements of stone size was corrected for an empirically determined magnification factor of 1.3.

Statistical analysis was done by means of regression analysis, the Chi-square test for trends in proportions, and the test for differences between proportions assuming binomial distributions.

Results

Four hundred and forty eight patients (109 male, 339 female; mean age 49.8 $\pm$ 14 [range: 21-88]) underwent OCG. Opacification was found in 323 cases (72.1%) and nonvisualization in 125 (27.9%). Calcifications were found in 85 cases of 323 visualized gallbladders (26.3%). These results are summarized in Table 1 together with the calcification patterns.

Table 1: gallbladder opacification, stone calcification and buoyancy recorded at oral cholecystography in 448 symptomatic gallstone patients

Feature	No. of patients	Percentage
Gallbladder		
-opacification	323	72.1
Gallstones		
-calcification	85	26.3
completely	30	35.3
rim ≤2mm	24	28.2
rim >2mm	13	15.3
core	13	15.3
not recorded[1]	5	5.9
-buoyancy	20	4.5

1) OCG performed in another hospital

Between the sexes there was no significant difference in opacification (69.7% [males] vs. 74.6% [females]; p=0.31) and calcifications (31.6% [males] vs. 24.1% [females]; p=0.19).

Stones were calcified in 35.3% of the solitary stones [36/102] and in 18.2% of multiple stones [49/269] ($p<0.0005$). Mean diameter of the largest stone was on OCG 17.3 ± 11mm [range: 3-65]; median=15mm.

The distribution of number of stones is depicted in Table 2. With US, solitary stones were found in 30.1% of all 448 cases and 33.1% of the 323 gallbladders, visualising at OCG. Mean diameter of the largest stone measured with US, was 14.2 ± 8mm [range: 3-45]; median=12mm.

Patients ≤40 yrs and >40 yrs had opacified gallbladders in 69.3% [88/127] and 73.2% [235/321] of the cases, respectively (p=0.40). Patients ≤40 yrs and >40 yrs had calcified stones in opacified gallbladders in 16.9% [15/89] and 29.9% [70/234] of the cases, respectively ($p<0.02$).

Discussion

US is the preferred diagnostic tool for detecting gallstones, for it is noninvasive and -unlike OCG- simple to perform, lacks ionising radiation and is independent of hepatic function [12,13]. Moreover, US is slightly more sensitive than OCG [14] (Table 2). Still, OCG is very reliable in determining gallstone size and number [14]. It also provides information

Table 2: distribution of number of stones at oral cholecystography (OCG) and the corresponding findings at ultrasonography (US) in 323 visualized gallbladders of 448 symptomatic patients

Number of stones	Number of patients on OCG (%)	Number of patients on US (%)
0	54 [16.7]	18 [5.6][1]
1	102 [31.6]	107 [33.1]
2	41 [12.7]	41 [12.7]
3	13 [4.0]	20 [6.2]
4	12 [3.7]	11 [3.4]
5	8 [2.5]	23 [7.1]
6-10	24 [7.4]	27 [8.4]
>10	57 [17.6]	65 [20.1]
Not specifically stated	12 [3.7]	11 [3.4]
Total	323	323

1) grit (concretions <3mm) [6], polyps [4], sludge [2], adenomyomatosis [1], passsed stones [5].

on the functional state of the gallbladder, information which is necessary for several nonsurgical treatment modalities for symptomatic gallstones.

We analyzed the radiographic findings of 448 symptomatic gallstone patients. It is one of the largest prospective clinical studies available in the US era. Moreover, these data were double-checked with US in all cases. That different radiologists interpreted the OCGs most probably did not influence results, because it has been demonstrated that there is little inter-observer variety in assessment of visualization of the gallbladder and opaqueness of gallstones [10].

We found an overall opacification rate of 72.1%, which is comparable with two epidemiologic studies in Italy [10,15]. Although Mujahed et al. found an overall visualization rate of 91.7%, it must be borne in mind that he used a different OCG regimen [16]: at day 1 of his 2-day examination, 75.2% of the gallbladders opacified which is indeed comparable with our data. We also found that age is not a determinant of visualization, which was also found by the Rome group [10].

We demonstrated an overall calcification rate of 26.3%, a percentage also largely comparable with the Rome group, which found radiopacity in 29.1% of the cases [10]. It is also in accordance with the clinical impression that radiolucent prevail over radiopaque stones

[17]. We found that elderly are more likely to have calcified gallstones than younger patients, which is in accordance with Bell's chemical analysis of gallstones [18]. However, unlike Bell and others [19], we, like the GREPCO-study, were not able to demonstrate a significant larger calcification rate in men than in women. This is most probably caused by the fact that radiologic studies do not entirely reflect the chemical structure of the gallstones, because not all calcifications are shown at radiography [20]. On the other hand, the discrepancy may be due to selection. Bell found a radiopaqueness in 50% of patients coming to cholecystectomy and in his manuscript he already noted that this rate was considerably higher than reported elsewhere [18]. He argued that radiopaque stones were more likely to be detected than radiolucent stones, which was true because his study was performed in the pre-US era. Sutor and Wooley also used gallstones removed at cholecystectomy [19], possibly explaining the difference.

We have found that multiple stones prevail over solitary stones with both OCG and US, which is in accordance with the clinical impression [17]. This was also found in a another clinical study performed by Brink, who investigated the contents of extirpated gallbladders [21]. Epidemiologic studies, however, demonstrate solitary stones in 40.5-50.9% of the OCGs [10,22] and 45% of the USs [23]. This discrepancy between clinical and epidemiologic studies suggests that multiple stones are more likely to cause biliary symptoms than solitary stones. This impression is in accordance with the findings of the National Cooperative Gallstone Study, where patients with multiple stones had more biliary pain before entering the study and were more likely to develop symptoms during the prospective follow-up [24].

Finally, to our knowledge, we are the first to report on the finding that solitary stones are calcified more often than multiple stones, which finding adds to the hypothesis that solitary and multiple stones have different etiologies [25].

Our finding that elderly patients are more likely to have calcified gallstones imply that these patients are less likely to profit from nonsurgical therapy. First, because all sorts of calcifications exclude them from oral and contact dissolution therapy [2-5]. Second, because calcifications of >2mm are contraindicated for ESWL [6,7]. And third, because stones with a calcified rim ≤ 2mm are even less likely to be cleared with ESWL than noncalcified stones [26]. In contrast to this, is the fact that rotary contact lithotripsy is able to treat all sorts of stones, including calcified ones [8]. This form of treatment, however, is invasive and not readily available in most clinics [27].

That elderly patients are less likely to be suitable for nonsurgical therapy is regrettable, because in these patients this form of treatment is most likely to be indicated and cost-effective [28].

References

1. Cole WH. Historical features of gallbladder disease: an imaging symposium. Radiology 1961;76:354-75.
2. Danziger RG, Hofmann AF, Schoenfield LJ, et al. Dissolution of cholesterol gallstones by chenodeoxycholic acid. N Engl J Med 1972;286:1-8.
3. Bachrach WB, Hofmann AF. Ursodeoxycholic acid in the treatment of cholesterol cholelithiasis. Dig Dis Sci 1982;27:737-61 & 833-56.
4. 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.
5. Leuschner U, Hellstern MD, Schmidt K, et al. Gallstone dissolution with Methyl tert-Butyl Ether in 120 patients. Efficacy and Safety. Dig Dis Sci 1991;36:193-9.
6. Sackmann M, Pauletzki J, Sauerbruch T, et al.The Munich gallbladder lithotripsy study: results of the first 711 patients. Ann Intern Med 1991;114:290-6.
7. Toom R den, Vergunst H, Nijs HGT, et al. Electromagnetic shock wave lithotripsy of gallbladder stones: a wide range of inclusion criteria. Am J Gastroenterol 1992;87:498-503.
8. Miller FJ, Rose SC, Buchi KN, et al. Percutaneous rotational contact biliary lithotripsy: initial clinical results with the Kensey Nash Lithotrite. Radiology 1991;178:781-5.
9. Paumgartner G, Carr-Locke DL, Roda E, et al. Biliary stones: non-surgical therapeutic approach. Gastroenterol Int 1988;1:17-24.
10. 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.
11. Berk RN. The problem of impaired firts-dose vizualisation of the gallbladder. AJR 1971;113:186-8.
12. Simeone JF, Mueller PR, Ferruci JT. Nonsurgical therapy of gallstones: implications for imaging. AJR 1989;152:11-7.
13. Maglinte DDT, Torres WE, Laufer I. Oral cholecystography in contemporary galstone imaging: a review. Radiology 1991;178:49-58.
14. Brakel K, Laméris JS, Nijs HGT, et al. Accuracy of ultrasound and oral cholecystography in assessing the number and size of gallstones: implications for nonsurgical therapy. Br J Radiol 1992;65:779-83.
15. Barbara L, Sama C, Morselli Labate AM, et al. A population study on the prevalence of gallstone disease. The Sirmione Study. Hepatology 1987;7:913-7.
16. Mujahed Z, Evans JA, Whalen JP. The nonopacified gallbladder on oral cholecystography. Radiology 1974;112:1-3.
17. Sherlock S. Diseases of the liver and biliary system (7th ed). Oxford: Blackwell Scientific Publications, 1985.
18. Bell GD, Dowling RH, Whitney B, et al. The value of radiology in predicting gallstone type when selecting patients for medical treatment. Gut 1975;16:359-64.
19. Sutor DJ, Wooley SE. A statistical survey of the composition of gallstones in 8 countries. Gut 1971;12:55-61.
20. Brakel K, Laméris JS, Nijs HGT, et al. Predicting gallstone composition with CT: in vivo and in vitro analysis. Radiology 1990;174:337-41.
21. Brink JA, Simeone JF, Mueller PR, et al. Physical characteristics of gallstones removed at cholecystectomy: implications for extracorporeal shock wave lithotripsy. AJR 1998;151:927-31.
22. Bainton D, Davies GT, Evans KT, et al. Gallbladder disease: prevalence in a South Wales industrial town. N Engl J Med 1976;294:1147-9.
23. Jensen KH, Jorgenson T. Incidence of gallstones in a Danish population. Gastroenterology 1991;100:790-4.
24. Thistle JL, Cleary PA, Lachin JM, et al. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med 1984;10:171-5.

25. Erpecum KJ van, Berge Henegouwen GP van, Stoelwinder B, et al. Bile concentration is a key factor for nucleation of cholesterol crystals and cholesterol saturation index in gallbladder bile of gallstone patients. Hepatology 1990;11:1-6.
26. Schoenfield LJ, Berci G, Carnovale RL, et al. The effect of ursodiol on the efficacy and safety of extracorporeal shock-wave lithotripsy of gallstones: The Dornier National Biliary Lithotripsy Study. N Engl J Med 1990;323:1239-45.
27. Plaisier PW, Hul RL van der, Terpstra OT, et al. Current treatment modalities for gallstone disease. Am J Gastroenterol 1993;88:633-9.
28. Bass EB, Steinberg EP, Pitt HA, et al. Cost-effectiveness of ESWL vs. cholecystectomy for symptomatic gallstones. Gastroenterology 1991;101:189-99.

Unexpected difficulties in randomizing patients into a surgical trial: experiences from a prospective study comparing extracorporeal shock wave lithotripsy with open cholecystectomy

P.W. Plaisier, M.Y. Berger, R.L. van der Hul, H.G.T. Nijs, R. den Toom, O.T. Terpstra, H.A. Bruining

World J Surg (accepted for publication)

Abstract

Shortly after extracorporeal shock wave lithotripsy (ESWL) was introduced as a promising new treatment modality for gallstone disease, a randomized controlled study was performed to assess the (cost-) effectiveness of ESWL, compared to open cholecystectomy, the gold standard. During the performance of this study it was found that in a 3-years intake period, only 8.3% (37/448) of the patients could be entered into the trial. Three factors could be identified, which hampered patient accrual. First, restricted eligibility for ESWL (and thus for the study), which could not have been predicted on the data provided in the literature. Second, the introduction of laparoscopic cholecystectomy. Third, strong patient's preference, inhibiting randomization. All three mechanisms could not have been predicted during the design phase of the study. It is concluded that it is not always feasible to conduct a randomized study in surgery due to unforseen circumstances. Entering patients into surgical trials is difficult in quickly evolving fields of surgery, such as the management of gallstone disease. Acquiring informed consent is also difficult when treatment characteristics are very divergent. A good randomized controlled study on the effects of laparoscopic cholecystectomy will, therefore, most probably never be performed.

Introduction

Gallstone disease is an important clinical problem in western countries and traditionally considered a surgical problem. It is generally agreed that open cholecystectomy is the standard therapy for symptomatic gallstones [1,2]. Still, much effort is put into the development of alternative, preferably non-invasive, treatment modalities for gallstone disease [3]. One of these recently developped, non-invasive, treatment modalities for gallstone disease, is extracorporeal shock wave lithotripsy (ESWL). The initial results of ESWL of gallbladder stones were very promising [3-5].

Because of the possibly tremendous clinical and economical consequences of ESWL, we initiated a study on the effects of this new technique and its cost-effectiveness [6]. We choose a randomized controlled design, since randomized studies are considered to provide the most reliable information for proper evaluation of new techniques [7-14]. Moreover, in this way, discussions could be avoided, similar to the ones that developed after the general adoption of ESWL of kidney stones: this treatment modality almost completely displaced open surgery although a randomized study never was performed [15-17].

During the performance of our study, several problems were encountered in acquiring adequate patient accrual. In this paper we describe the difficulties we met in patients' accrual.

Patients and methods

To assure optimal patient accrual for our randomized study, a surgical outpatient clinic solely for gallstone patients was started. In a 3-year intake period, 596 patients visited this outpatient clinic.

All patients were analyzed according to protocol: of all patients a history was taken and a physical examination performed. Using the Roma Working group definition [18], patients were diagnosed as either 'symptomatic' or 'a-symptomatic'. Asymptomatic patients were excluded from further analysis and did not receive therapy. With symptomatic patients the different therapeutic options were discussed. These patients underwent further analysis: laboratory tests and radiological examination.

Laboratory tests consisted of liver function tests for screening on common bile duct stones and radiological examination consisted of ultrasonography (US) and oral cholecystography (OCG). An OCG was not performed, if the patient refused ESWL as a therapeutic option or if a previous US examination already excluded the patient from ESWL

(Chapter 4; Table 1).

At the end of analysis, all eligible patients, were informed about the study and asked for consent to be randomized. When informed consent was given, therapy was randomly assigned and self-administered health questionnaires and interviews were taken at 0, 3, 6, 12, 18 and 24 months. If patients did not want to participate in the study, they received the therapy of their choice.

Results

From April 1989-April 1992, 596 (successively : 238, 179 and 179) patients visited the outpatient clinic. Their characteristics are presented in Table 1. Three hundred and sixty seven patients (61.6%) were referred by their general practioner, 141 (23.7%) by specialists and 88 (14.8%) visited on their own initiative. Five hundred and eighty four patients (98.0%) underwent US and 345 (57.9%) OCG.

Table 1: patient characteristics in 596 patients referred to the University Hospital 'Dijkzigt' for gallstone management

age	49.1 ± 14.5
range	19 - 88
♂/♀-ratio	0.36 [158/438]
Q-index[1] >27.0	175/498 [35.1%]
ASA[2] III/IV	19 [3.2%]
symptomatic	499 [83.7%]
total	596

1) Q-index : Quetelet index : weight [kg]/(length [m])^2

2)ASA : classification of anaesthesia risk according to the American Society of Anaesthesiologists

Twelve patients discontinued analysis and 96 patients were not symptomatic (Figure 1). Of 488 patients, potentially randomizable, 310 (69.2%) were excluded because they did not meet the entry criteria. Another 141 patients (31.5%) were excluded because they refused

random assignment of therapy. So, 37 patients (18, 12 and 7, respectively) consented in entering the study, which is 6.2% of the total number of analyzed patients and 7.6% of the patients potentially randomizable. Eighteen patients were randomized for cholecystctomy and 19 for ESWL.

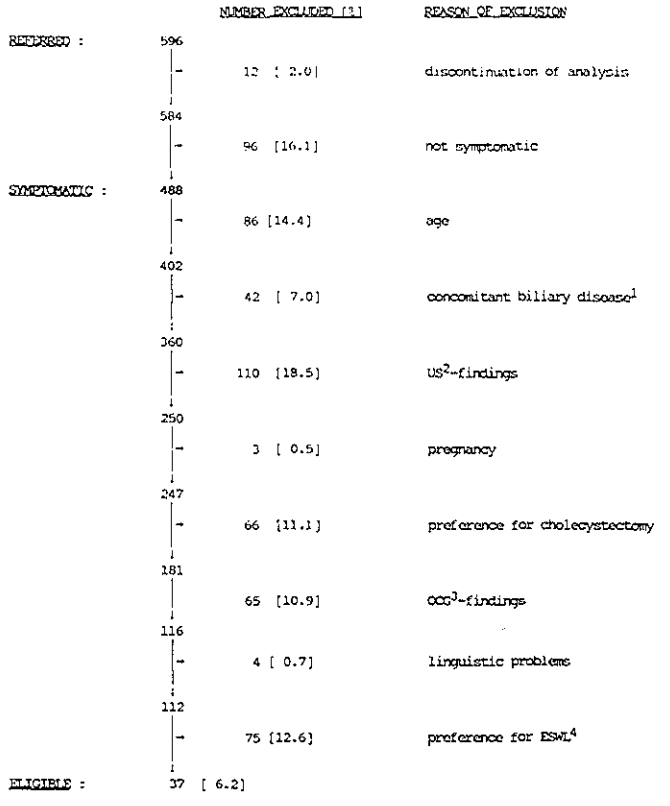

Figure 1: flow chart for not entering the study

1) cholecystitis, jaundice, cholangitis, pancreatitis, hepatitis or concomitant bile duct stones
2) US = ultrasonography
3) OCG = oral cholecystography
4) ESWL = Extracorporeal Shock Wave Lithotripsy
5) 8.3% of 488 potentially randomizable patients

Discussion

There is unanimous agreement that new treatment techniques should be introduced in a manner that allows proper evaluation [7]. Although randomized studies have specific problems, they are considered to provide the most reliable information for such evaluation

[7-14,19]. The mechanism of allocating patients to different treatment schemes by randomisation, is accepted almost without question now [10].

New surgical techniques are considered more difficult to evaluate than new drugs [16,20]. In fact, most clinical research in surgery, relies on comparison with historical or contemporary non-random controls [11]. One of the most striking examples of this phenomenon, is ESWL of renal and ureteric calculi, which completely displaced open surgery [15]. This development consequently led to much discussion, since no randomized study was ever performed [16,17]. When ESWL was introduced for the desintegration of gallbladder stones, it was therefore suggested that the proper assessment of the role of ESWL should be delt with in the context of a randomized trial [3].

During the performance of our study, only a minority of patients could be randomized. It should be noted here, that despite this poor patient entry, it was decided to continue the study. First, because interim-analysis showed some interesting points. Second, because five other hospitals decided to participate in the study. Third, because a large number of non-randomized patients were entered into the study. However, since this is besides the point of this manuscript, this is not discussed here.

Poor patient entry was caused by three mechanisms, which could not have been predicted when the study was designed. First, contrary to the data in the literature, eligibility for ESWL was found to be limited. Second, yet another alternative treatment of gallbladder stones was introduced during the performance of our study. Third, strong patient preference for one of the two treatment arms was encountered, which inhibited randomization.

Restricted eligibility for ESWL

Partial applicability was reported already by Sackmann and co-workers [4]. However, this was not considered a major obstacle for our study, for we had reasons to assume that our eligibility rate would be higher than that reported by the Munich group. First, because our entry criteria were much wider than those of the Munich group, especially with regard to the maximum number of stones (10 versus 3). Second, because another research group reported a randomisation rate of 57.1% in a trial comparable to ours [21]. Moreover, even at Sackmann's eligibility rate of 28%, accrual of 160 patients -estimated to be necessary to detect any clinically relevant differences in the two treatment options- was considered to be easily achieved in 3 years at our referral rate of approximately 200 patients per year.

The introduction of yet another alternative treatment

Shortly after our study was started, a new variant of classical cholecystectomy was introduced: laparoscopic cholecystectomy [22,23]. Compared to the 'open' technique, laparoscopic cholecystectomy is reported to have several advantages. It is accompanied by less morbidity and mortality and consequently by a reduction in duration of hospitalization, time to return to full activity and the need for analgetic drugs. Also for cosmetic reasons, laparoscopic cholecystectomy is more attractive. Laparoscopic cholecystectomy is considered the new gold standard now [24] even although this technique has not been studied in the context of a randomized trial.

Strong patient's preference

Many mechanisms may lead to strong patient's preference. Two mechanisms limited accrual in our case: adherence to new technologies and the divergent character of the two treatment arms. The lay press most probably reinforced these two mechanisms.

Adherence to new technologies

Emotional adherence to new technologies is considered a major obstacle for randomisation and it even becomes insurmountable if it has spread to the general public [13]. We even encountered this phenomenon twice: in the beginning of the study when patients specifically chose ESWL and in a later stage of our trial when patients specifically opted for the laparoscopic cholecystectomy.

The divergent character of the two treatment arms

Strong patient's preference also occurs when the treatment modalities studied are very divergent [25,26]. ESWL and cholecystectomy have indeed very different characteristics (Table 2) and since the outcomes of these characteristics were so clear to many patients, they specifically opted for a certain treatment modality and simply rejected random assignment. It has been recognized before that comparing treatment regimes with divergent characteristics is extremely difficult [27]: only 2% of eligible patients are recruited in breast cancer trials in the United States [28] and in a trial comparing mastectomy and conservation surgery in Great Britain, fewer than half of the eligible patients could be recruited [29]. Recently, some of the large trials comparing percutaneous transluminal coronary angioplasty (PTCA) and

coronary artery bypass graft (CBAG) have also stopped intake without having recruited the aimed number of patients [30].

Table 2: base line characteristics between cholecystectomy and extracorporeal shock wave lithotripsy (ESWL)

	Cholecystectomy	ESWL
outpatient procedure	-	+
general anaesthesia	+	-
curative	+	-
probability on stone recurrence	-	+
biliary colics after initial therapy	0%	35%
morbidity	10-30%	<5%
mortality	0.1-0.3%	0%
adjuvant treatment[1] required	-	+

1) orally administered bile acids.

In the field of gallstone management, a trial comparing laparoscopic cholecystectomy and the so-called 'mini-cholecystectomy' suffered from a high withdrawel rate after randomisation and this trial was eventually stopped because of difficult patient recruitment [31]. The only alternative to overcome this particular problem clearly would have been to randomize patients without their informed consent, analogously to the European Carotid Surgery Trial [32].

The role of lay press

The role of lay press in hampering patient accrual has been recognized before [29]. Also in our study, lay press played an important role in promoting patient's preference: in some popular magazines successes of ESWL and laparoscopic cholecystectomy were extremely exaggerated and the possibility of faillure and complications underestimated or not mentioned at all. Obviously, this promoted patient's preference to a large extent. As a consequence, the universal adoption of laparoscopic cholecystectomy has been merely patient driven [33,34], as a result of media exposure [35].

Conclusions

Our data confirm that proper information on the feasibility of a trial is not always available before it is started [35]. Our data also confirm that it is not always feasible to conduct a randomized study successfully because of inadequate patient accrual [9]. Furthermore, we confirmed that acquiring informed consent is much more difficult if treatment characteristics are very divergent and that comparing different forms of therapy in a randomized studies is hazardous in quickly evolving fields of surgery, such as the management of gallstone disease. It is, therefore, equally true that a prospective controlled study on the effects of laparoscopic cholecystectomy cannot be performed [7,36]. In such cases alternatives to randomized studies have to be used [8,13,26,37].

References

1. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989;158:174-8.
2. Soper NJ, Dunnegan DL. Summary of NIH consensus development conference "gallstones and laparoscopic cholecystectomy". World J Surg 1993;17:21.
3. Vergunst H, Terpstra OT, Brakel K, et al. Extracorporeal shock wave lithotripsy of gallstones: possibilities and limitations. Ann Surg 1989;210:565-75.
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. Burhenne HJ. The promise of extracorporeal shock-wave lithotripsy for the treatment of gallstones. AJR 1987;149:233-5.
6. Nijs HGT, Toom R den, Berger MY, et al. Extracorporeal shock wave lithotripsy versus cholecystectomy: the need for randomized clinical trials. J Lithotripsy Stone Dis 1991;3:112-3.
7. Neugebauer E, Troidl H, Spangenberger W, et al. Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. Br J Surg 1991;78:150-4.
8. Zelen M. A New design for randomized clinical trials. N Engl J Med 1979;300:1242-5.
9. Van der Linden W.Pitfalls in randomized surgical trials. Surgery 1980;87:258-62.
10. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. BMJ 1989;299:313-5.
11. Pollock AV. The rise and fall of the random controlled trial in surgery. Theor Surg 1989;4:163-9.
12. Russell PS. Commentary on 'The rise and fall of the random controlled trial in surgery'. Theor Surg 1989;4:169-70.
13. Olschewski M, Schumacher M, Davis KB. Analysis of randomized and nonrandomized patients in clinical trials using the comprehensive cohort follow-up study design. Controlled Clin Trials 1992;13:226-39.
14. Challah S, Mays NB. The randomised controlled trial in the evaluation of a new technology: a case study. Br Med J 1986;292:877-9.
15. Kahn RI. Early United States experience with the EDAP LT-01 piezoelectric shock wave lithotripter. J Lithotripsy Stone Dis 1989;1:224-30.
16. Dudley HAF. Stones, lithotripters, trials and arguments. BMJ 1986;292:846-7.
17. Wiser LC, Plain RH, Dossetor JB. Kidney stones and lithotripters: critical analysis of the introduction of extracorporeal shock wave lithotripsy into Canada. Can Med Assoc J 1990;143:1299-1303.
18. Paumgartner G, Carr-Locke DL, Roda E, et al. Biliary stones: non-surgical therapeutic approach. Gastroenterol Int 1988;1:17-24.
19. MacIntyre IMC. Tribulations for clinical trials: poor recruitment is hampering research. BMJ 1991;302:1099-1100.
20. Spodick DH. Numerators without denominators: there is no FDA for the surgeon. JAMA 1975;232:35-6.
21. 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 1991;1:122-32.

22. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991;324:1073-8.
23. Cushieri A, Dubois F, Mouiel J, et al. The European experience with laparoscopic cholecystectomy. Am J Surg 1991;161:385-7.
24. Schirmer BD, Edge SB, Dix J, et al. Laparoscopic cholecystectomy: treatment of choice for symptomatic cholelithiasis. Ann Surg 1991;213:665-77.
25. Oetinger W, Beger HG. Commentary on 'The rise and fall of the random controlled trial in surgery'. Theor Surg 1989;4:170.
26. Angell M. Patient's preferences in clinical trials. N Engl J Med 1984;310:1385-7.
27. BARI, CABRI, EAST, GABI, AND RITA: coronary angioplasty on trial [editorial]. Lancet 1990;335:1315-6.
28. DeVita VT. Breast cancer therapy: exercising all our options. N Engl J Med 1989;320:527-9.
29. Jack WJL, Chetty U, Rodger A. Recruitment to a prospective breast conservation trial: why are so few patients randomised? BMJ 1990;301:83-5.
30. Breeman A, Serruys PW, Brand MJBM, et al. Percutane transluminale coronaire angioplastiek versus coronaire chirurgie bij meervatslijden, een overzicht. Deel 2. Ned Tijdschr Cardiol 1992;8:238-46.
31. Barkun JS, Barkun AN, Sampalis JS, et al. Randomised controlled trial of laparoscopic versus mini cholecystectomy. Lancet 1993;340:1116-9.
32. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1235-43.
33. Emberton M, Howerton R. Laparoscopic cholecystectomy. BMJ 1992;304:777.
34. Miles RH, Carballo RE, Prinz RA, et al. Laparoscopy: the preferred method of cholecystectomy in the morbidly obese. Surgery 1992;112:818-23.
35. Friedman LM, Furberg CD, DeMets DL. Fundamentals of clinical trials. Massachusetts, PSG Publishing Company Inc, 1985.
36. Carey LC. Cholecystectomy- A new standard. Ann Surg 1992;216:617.
37. Hellman S, Hellman DS. Of mice but not men: problems of the randomized clinical trial. N Engl J Med 1991;324:1585-9.

Quality of life and the course of biliary and gastrointestinal symptoms after laparoscopic and conventional cholecystectomy

P.W. Plaisier, R.L. van der Hul, H.G.T. Nijs, R. den Toom, O.T. Terpstra, H.A. Bruining

submitted for publication

Abstract

A prospective study was performed to evaluate quality of life and the course of biliary and gastrointestinal symptoms after laparoscopic cholecystectomy (LC) and conventional cholecystectomy (CC) for uncomplicated, symptomatic biliary disease. Fourteen patients underwent LC and 17 patients underwent CC. Quality of life questionnaires and symptom profiles were taken before and at 3, 6, 12, 18 and 24 months after therapy. Pain diaries covered the periods 0-3, 3-6, 6-12 and 12-18 months. Median follow-up was 12 and 24 months for LC and CC, respectively. Quality of life significantly improved after 6 months in the LC-group and to a similar degree after 12 months in the CC-group. Stomach swelling, fatty food upset and nausea improved significantly at 3, 6 and 6 months after LC and at 6, 18 and 24 months after CC, respectively. Vomiting and belching had a tendency to improve slightly, while pyrosis, constipation and diarrhoea did not improve in both groups. Biliary pain was cured in 81% of the patients (25/31) directly after cholecystectomy. Biliary pain was not reported after 6 months after treatment. Cholecystectomy improves quality of life and cures nausea, fatty food upset, stomach swelling and biliary pain. LC improves quality of life and symptomatology to the same degree in an earlier stage than CC. Therefore, with respect to quality of life and abdominal symptoms, LC is preferable to CC for the treatment of uncomplicated symptomatic gallstones.

Introduction

Any form of elective surgery is directed primarily to improvement of quality of life, i.e. the relief of disability, discomfort and disfigurement [1,2]. Especially in the treatment of symptomatic gallstones, improving the patient's quality of life should be the most important aim of intervention [3]. We studied the effects of cholecystectomy on quality of life. We aiso studied its effects on the course of biliary and gastrointestinal symptoms. Finally, we studied differences between the effects of laparoscopic cholecystectomy as compared to conventional cholecystectomy, the gold standard [4,5].

Patiends and methods

Thirty one patients with uncomplicated, symptomatic biliary stone disease were recruited from a surgical outpatient biliary clinic, in the period January 1990 - January 1993. Patients were diagnosed as 'symptomatic' according to the Roma Working Team-definition [6]. With this definition, symptomatic stone disease is characterized by acute biliary pain involving one or more episodes of abdominal pain (usually epigastric or right upper quadrant) lasting more than 15 minutes but less than five hours. The absence of biliary complications was demonstrated by physical examination, a white blood cell count, liver function tests and ultrasonography of the abdomen.

Laparoscopic cholecystectomy (LC)

Fourteen patients, 1 man and 13 women, underwent LC. Mean age was 45 years (range 30-68). Median Quetelet-index was 24.8 kg/m^2 (range 20.5-38.1). LC was performed via four abdominal incisions after insufflation of carbon dioxide. It was performed under general anesthesia, as an inpatient procedure. Intra-operative cholangiography was not performed.

Conventional cholecystectomy (CC)

Seventeen patients, 3 men and 14 women, underwent CC. Mean age was 49 years (range 30-67). Median Quetelet-index was 24.5 kg/m^2 (range 19.5-38.1). CC was performed by laparotomy, via an oblique subcostal incision. It was performed under general anesthesia, as an inpatient procedure. Intra-operative cholangiography was not performed.

Follow-up

Follow-up consisted of self-administered health questionnaires, symptom profiles and pain diaries. A Dutch translation of the Nottingham Health Profile was used for the quality of life assessment [7]. This health profile questionnaire consists of 6 so-called domains, being explored in 38 questions requiring a 'yes' or 'no' answer (dichotomous). If all questions are answered 'yes', the patient scores highest, but is considered having the least quality of life. 'Health gain' can be defined as the decrease in median score (ergo: the median decrease in positively answered questions). On the symptom profiles, the patients had to score whether they suffered from the following gastrointestinal complaints: nausea, fatty food upset, vomiting, stomach swelling, pyrosis, belching, constipation and diarrhea. Scoring was performed on a semi-quantative scale (absent, mild, moderate or severe). On the self-administered 'pain diaries', patients had to fill out the date, the duration and severity (mild, moderate or severe) of pain, when experiencing biliary pain. Patients experiencing pain had to indicate specifically whether this pain was similar or different from the pain they experienced before cholecystectomy. Health questionnaires and symptom profiles were taken before therapy (t=0) and at 3, 6, 12, 18 and 24 months after therapy. Pain diaries covered only the post-operative phase, i.e. 0-3, 3-6, 6-12 and 12-18 months. Health questionnaires, symptom profiles and pain diaries were sent by mail and double-checked by telephone 1 month after receipt.

Statistics

Statistical analysis was done with the Kruskal-Wallis test, Wilcoxon rank test and a standard test for comparing proportions assuming binomial distributions. A p-value of <0.05 was considered statistically significant.

Results

Laparoscopic cholecystectomy

Mean and median hospitalization time, including the days of admission and discharge, were 5 days (range: 4-9). No LC was converted into CC. Postoperatively, no complications occurred and there was no mortality. Mean follow-up was 13.1 months (median : 12; range: 3-24). No patient was lost to follow-up.

Conventional cholecystectomy

Mean and median hospitalization time, including the days of admission and discharge, were 9 days (range: 6-12). Postoperatively, one patient had to be observed for 6 hours at an intensive care unit for an epileptic insult. One patient suffered from wound dehiscence, treated conservatively. Two patients complained of persistent scar pain. There was no mortality. Mean follow-up was 23.6 months (median : 24; range : 18-24). No patient was lost to follow-up.

Quality of life

NHP-questionnaires were returned and filled out correctly in 96.5% (165/171) of the cases. It was found that the median overall percentage of items answered positively, decreased to the same degree in both treatment groups after therapy (Figure 1). This decrease, however, became significant 6 months after LC and and only 12 months after CC. Health status remained significantly better hereafter in both groups (not shown). There was no significant difference at baseline between the two treatment groups.

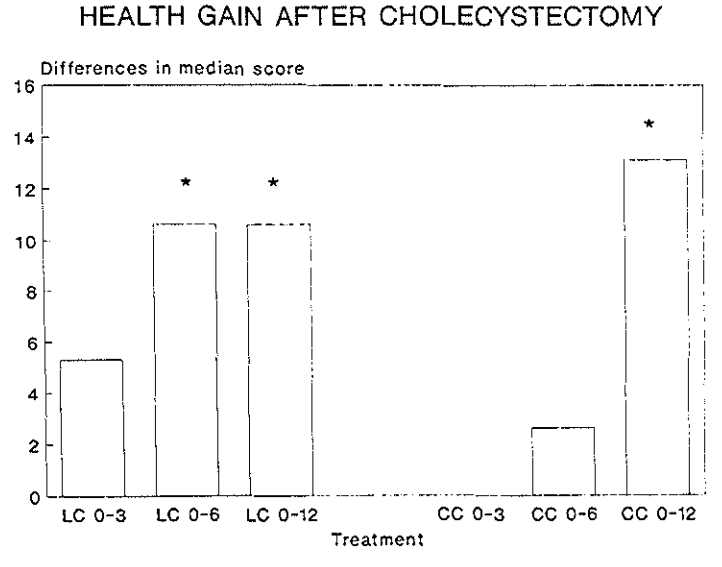

Figure 1: median total scores (in %) on Nottingham Health Profiles after; on the abscissa: months

LC: laparoscopic cholecystectomy; CC: conventional cholecystectomy; * = $p<0.05$; compared with t=0

Gastrointestinal symptoms

The reported frequencies of nausea, fatty food upset and stomach swelling in the course of 1 year, are depicted in Table 1. Both fatty food upset and nausea improved significantly and consistently after 6 months in the LC-group but not in the CC-group. Here, a significant improvement in fatty food upset and nausea occurred only after 18 and 24 months, respectively (not shown). Stomach swelling improved significantly after 3 and 6 months in the LC and CC-group, respectively. Vomiting and belching improved only slightly in both treatment groups, but improvements were statistically insignificant. Reported frequencies of pyrosis, constipation and diarrhea did not change after therapy. There were no significant differences in reported symptoms between the two treatment arms at baseline.

Table 1: reported frequencies (in %), graded moderate or severe, of fatty food upset, nausea and stomach swelling after laparoscopic (n=14) and conventional cholecystectomy (n=17)

time (months)	fatty food upset		nausea		stomach swelling	
	LC	**CC**	**LC**	**CC**	**LC**	**CC**
0	47	37	47	37	33	47
3	33	21	8[a]	16	0[b]	32
6	0[b]	33	0[b]	17	10	11[a]
12	0[b]	16	0[b]	26	0[b]	11[b]

LC = Laparocopic cholecystectomy; CC = conventional cholecystectomy

a) $p<0.05$; compared with t=0 ; b) $p<0.02$; compared with t=0

Biliairy pain

Post-cholecystectomy biliary pain was found in 5 patients in the CC-group (29%) and 1 patient (7%) in the LC-group. This difference was not statistically significant ($p=0.12$) In the CC-group, 4 patients complained of 2-4 and 1 patient of 11 pain episodes, respectively. The LC-patient reported only 1 episode. Pain episodes were considered mild, moderate or severe in 29, 48 and 24%, respectively. No biliary pain was reported after 6 months after cholecystectomy.

Discussion

LC has revolutionized clinical practice to a great extent and it has been claimed already that LC is the new gold standard for symptomatic gallstone disease [8]. However, well-controlled studies are unavailable [5] and there is little or no prospect that good randomized studies will ever be performed [9]. The one available randomized study was hampered by a significant age difference between the two studied groups [10].

The few available controlled studies all have some drawbacks. First, they usually used historic controls [11-13]. Second, they emphasized on complications and mortality [12,13]. Because both LC and CC are accompanied by relatively low morbidity and mortality rates, these rates are insensitive and, therefore, inappropriate to detect any differences between the two treatment arms in small series of patients [1,14,15]. Third, they also focused on operative time, hospitalization time and use of analgesia [11], which is only partially of interest to the patient.

We studied LC prospectively as compared to CC, which has been the standard operation for gallstone disease for more than a century [4]. We emphasized on quality of life, because this seems to be of major interest to the patient. Moreover, especially minimally invasive surgery is an area well suited for quality-of-life research [15] and in fact, improving quality of life is always the most important aim in the elective treatment of symptomatic gallstones [3].

We chose the Nottingham Health Profile, since it is well validated and one of the most widely used general measures of quality of life [14]. Moreover, it can be easily administered by mail and makes relatively small demands on patient time and effort [14-16]. Because there was a significant difference in follow up between the two treatment groups ($p=0.03$), we analyzed only the data of 1 year in the LC-group.

We found that both therapies are safe, cure biliary colics and improve both quality of life and three gastrointestinal complaints, i.e. fatty food upset, nausea and stomach swelling. These data are in accordance with data recently published in a larger series of patients [17]. We also found that symptoms may persist after cholecystectomy, which is in agreement with the literature [18-21]. Because of the specific design of the pain diaries and symptom questionnaires, we could confirm that the reported symptoms were usually mild and of short duration [18-21]. We, therefore, reconfirmed that cholecystectomy is justified as a treatment of uncomplicated symptomatic gallstone disease.

Compared with CC, we demonstrated that LC improves quality of life significantly earlier. This was also the case with fatty food upset, nausea and stomach swelling. Finally, we confirmed that LC caused a marked reduction in hospitalization time.

Drawback of our study is that it was not randomized and that the number of studied patients is relatively limited. Our study could not be designed as a randomized study, because it was initiated in a phase where we could not constantly dispose of a laparoscopic set. Consequently laparoscopy could not be planned and in fact it was unpredictable what treatment hospitalized patients would get. Still, we doubt whether randomization would have been possible: when a laparoscopic set were constantly available, patients would simply refuse random assignment of treatment and chose LC. Despite this, the present study was prospective, controlled and has a relatively long follow up. We could, therefore, provide more circumstantial evidence that LC is superior to CC.

References

1. Bunker JP, Wennberg JE. Operation rates, mortality statistics and the quality of life. N Engl J Med 1973;289:1249-51.
2. Goligher JC. Judging the quality of life after surgical operations. J Chron Dis 1987;40:631-3.
3. Eypasch E. Troidl H, Wood-Dauphinée S, et al. Quality of life and gastro-intestinal surgery: a clinimetric approach to developing an instrument for its measurement. Theor Surg 1990;5:3-10.
4. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989;158:174-8.
5. National Institutes of Health consensus development conference statement on gallstones and laparoscopic cholecystectomy. Am J Surg 1993;165:390-6.
6. Paumgartner G, Carr-Locke DL, Roda E, et al. Biliary stones: non-surgical therapeutic approach. Gastroenterol Int 1988;1:17-24.
7. Hunt SM, McEwen J, McKenna SP. Measuring health status. London: Croom Helm, 1986.
8. Schirmer BD, Edge SB, Dix J, et al. Laparoscopic cholecystectomy: treatment of choice for symptomatic cholelithiasis. Ann Surg 1991;213:665-77.
9. Neugebauer E, Troidl H, Spangenberger W, et al. Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. Br J Surg 1991;78:150-4.
10. Trondsen, E, Reiertsen O, Andersen OK, et al. Laparoscopic and open cholecystectomy: a prospective, randomized study. Eur J Surg 1993;159:217-21.
11. Soper NJ, Barteau JA, Clayman RV, et al. Comparison of early postoperative results for laparoscopic versus standard open cholecystectomy. Surg Gynecol Obstet 1992;174:114-8.
12. Barkun JS, Barkun AN, Meakins JL et al. Laparoscopic versus open cholecystectomy: the Canadian experience. Am J Surg 1993;165:455-8.
13. Williams LF, Chapman WC, Bonau RA, et al. Comparison of laparoscopic cholecystectomy with open cholecystectomy in a single center. Am J Surg 1993;165:459-65.
14. O'Boyle CA. Assessment of quality of life in surgery. Br J Surg 1992;79:395-8.
15. Fraser SCA. Quality-of-life measurement in surgical practice. Br J Surg 1993;80:163-9.
16 O'Brien BJ, Buxton MJ, Ferguson BA. Effectiveness of heart transplant programmes: quality of life data and their relationship to survival analysis. J Chron Dis 1987;40(suppl1):137S-53S.
17. Vander Velpen GC, Shimi SM, Cushieri A. Outcome after cholecystectomy for symptomatic gallstone disease and effect of surgical access: laparoscopic v open approach. Gut 1993;34:1448-51.

18. Ros E, Zambon D. Postcholecystectomy symptoms: a prospective study of gall stone patients before and two years after surgery. Gut 1987;28:1500-4.
19. Gilliland TM, Traverso LW. Modern standards for comparison with alternative treatments for symptomatic cholelithiasis with emphasis on long term relief of symptoms. Surg Gynecol Obstet 1990;170:39-44.
20. Bates T, Ebbs SR, Harrison M, et al. Influence of cholecystectomy on symptoms. Br J Surg 1991;78:964-967.
21. Konsten J, Gouma DJ, Meyenfeldt MF von, et al. Long-term follow-up after open cholecystectomy. Br J Surg 1993;80:100-2.

Current role of extracorporeal shockwave therapy in surgery

P.W. Plaisier, R.L. van der Hul, O.T. Terpstra, H.A. Bruining

Br J Surg 1994;81:174-81

Abstract

In urology the introduction of extracorporeal shockwave therapy brought a revolutionary change in the management of urinary calculi. This inspired the introduction of shockwave therapy in several fields of surgery; it has been applied as a potential alternative to several operative procedures, but is still experimental. So far, the major application of shockwave therapy has been lithotripsy of stones in the gallbladder, common bile duct, pancreatic duct and salivary gland ducts. Other applications are in the non-operative management of bone healing disturbances and in the inhibition of tumour growth. Steps towards selective thrombus ablation and pretreatment of heavily calcified arteries, have also been made. In this review, the applications of extracorporeal shockwave therapy in several areas of surgery are discussed. It is concluded that, for selected patients, shockwave therapy may serve as a useful addition to the surgical armamentarium.

Introduction

In 1980 the first clinical experience with extracorporeal shockwave therapy for the treatment of kidney stones was reported [1]. Nowadays, it is the therapy of choice in the case of urolithiasis and surgical treatment is restricted to fewer than 5 per cent of patients [2]. After good results in urology, shockwave therapy has been applied to other calculi, such as stones in the gallbladder, common bile duct (CBD), pancreatic duct, and salivary gland. Other applications are currently being tested. In this paper the current role of shockwave therapy in surgery is discussed; shockwave therapy treatment of stones is referred to throughout as lithotripsy.

Technical aspects and principles

Shockwaves can be generated by three methods: underwater electrostatic spark-gap discharge, electromagnetic generation and piezo-electric generation [3,4]. Approximately 20 different shockwave therapy devices are currently available and the initial water immersion bath has been largely replaced by a compressible water bag.

Shockwaves are characterized by their ultrashort high-pressure amplitudes with a steep onset and gradual decay; they obey the physical laws of acoustics. Shockwaves are generated in water and may travel through the human body without causing tissue damage, because both water and body tissue have a similar acoustic impedance. However, when such waves encounter an abrupt change of acoustic impedance, for instance at the interface of body tissue and a stone, energy is released. This causes tear and shear forces which, together with the formation of cavitation bubbles on the surface of a calculus, finally lead to progressive stone disintegration [5,6].

Objective comparisons of the working capacity of the different machines are considered difficult and are consequenltly rarely performed and contradictory [7-10]. To date the lithotriptors available can achieve disintegration of stones in vitro to a similar degree, which is independent of their method of shockwave production [7,8] and similar results are expected in clinical use [7]. However, while electromagnetic and piezoelectric devices have higher retreatment rates than electrohydraulic systems [11], the former have lower complication rates and allow lithotripsy sessions to be less painful [8,11]. Generally, the success rate in extracorporeal shockwave therapy is determined by entry criteria, treatment schemes, the lithotriptor used and experience of the physicians [8,12,13].

1. Hepatobiliary and pancreatic disease

1.1 gallbladder stones

Gallstone disease is an important clinical problem with tremendous economic concequences [14,15]. Approximately 10 per cent of the adult population in Western countries have gallstones [16,17]. Only a minority of such patients (10-15 per cent) develop symptoms [18,19] and it is generally agreed that only symptomatic gallstones require therapy [19-22]. Removal of the gallbladder is the 'gold standard' (because of its curative nature [19,23]), but is associated with considerable morbidity and mortality rates: 10-30 and 0.1-0.6 per cent, respectively [23-25]. Because of this, much effort has been put into the development of less invasive treatment modalities for gallstones. One of these is shockwave therapy.

The first succesfull shockwave treatment of patients with gallstones was reported in 1986 [26] and the results of the first large series of patients were published two years later [27]. These results were impressive; with minimal complications, 91 per cent of patients were free from stones 12-18 months after treatment. The selection criteria initially suggested by the Munich group, gradually became less strict [28-45]. Even slightly calcified stones [31,32] and largely calcified calculi have been successfully treated [33-35]. Major advantages of extracorporeal shockwave therapy are that it can be performed on an outpatient basis, requires only intravenous analgesia and is accompanied by minimal morbidity (Table 1). To date, no associated death has been reported.

Much experience has been gained now with gallstone lithotripsy [33-45] and more than 30,000 patients have been treated worldwide [46]. Nevertheless, it has become apparent that shockwave therapy will play only a minor part in the management of gallstone disease. Its limited role has been determined by two factors: limitations of shockwave treatment itself and the introduction of laparoscopic cholecystectomy.

The limitations of the technique itself are fivefold. First, extracorporeal shockwave therapy is applicable to only a minority of patients because only 10-53 per cent meet lithotripsy entry criteria [13]. Second, lithotripsy requires adjuvant treatment to dissolve stone fragments, such as orally administered bile acids. Third, the good results initially reported have not been reproduced and overall results must be considered moderate at best: on reviewing the literature Nahrwold found a mean 1-year stone clearance rate of 58 per cent [47], although reported stone-free rates at 12 months vary considerably (30-78 per cent) as shown in Table 1. Fourth, shockwave therapy is inevitably associated with the possibility of

stone recurrence, estimated to be approximately 20 per cent at 4 years [48]. Finally, lithotripsy is not cost-effective [49-51], except perhaps for elderly patients with a small stone load [52]. However, the most important factor determining the limited role of gallstone lithotripsy is laparoscopic cholecystectomy. This technique was introduced during the clinical evaluation phase of extracorporeal shockwave therapy and was adopted worldwide because of its apparent advantages over conventional cholecystectomy [53,54]. As a consequence, shockwave treatment is now indicated only for patients of high surgical risk and for those who refuse operation.

At present, patients with a 1-2 cm solitary radiolucent stone in a functional gallbladder benefit most from lithotripsy [44,45,55]. It should also be noted that, from a palliative point of view, extracorporeal shockwave therapy is very justifiable. It has been convincingly demonstrated that lithotripsy of gallstones significantly reduces episodes of biliary pain in most patients [52,56] and improves quality of life in general [52,57,58], independent from total stone clearance.

1.2 common bile duct stones

Stones in the CBD may present as the first sign of gallstone disease, or after cholecystectomy, with or without CBD exploration. Surgical bile duct exploration is an accepted treatment, but carries a considerable mortality rate that may be as 8 per cent in elderly high-risk patients [27,59,60]. In such patients, endoscopic sphincterotomy is the treatment of choice [61-63].

In about 10 per cent of patients it is not possible to remove stones from the CBD endoscopically [61,64,65], because of a discrepancy between the diameter of the stone and the bile duct, the presence of duodenal diverticula or previous abdominal surgery, such as that involving a Roux-en-Y reconstruction. In such cases extracorporeal shockwave therapy may offer an attractive alternative to surgery. The first successful shockwave treatment of CBD stones was performed in 1986 [26] and the first large series of patients treated so treated was published in 1989 [65]. Successful treatment of intrahepatic stones is also feasible [66-69].

Much experience with lithotripsy of CBD stones, has been gained to date [49,65-80]. Fragmentation is achieved in the majority of cases and stone clearance rates of up to 88 per cent have been reported (Table 1). Although some authors perform shockwave therapy of

CBD stones under ultrasonographic guidance [68,74,77,81], most consider access to the bile duct an imperative prerequisite [82]. Such access, achieved either endoscopically or percutaneously, provides both an entrance for fluoroscopic contrast agent and facilitates fragment clearance after lithotripsy, preventing iatrogenically induced pancreatitis or cholangitis. Additional measures, such as lavage and/or endoscopic or percutaneous extraction are necessary in 50-75 per cent of patients [49,65,67,69,71,72,78,82].

A major advantage of extracorporeal shockwave therapy of CBD stones is that morbidity rates are low (Table 1). Most minor complications, such as hematuria and hemobilia resolve within a few days [65,71,76] and serious complications, such as cholangitis, may often be regarded as an exacerbation of a pre-existing infection [65,67,71]. The reported mortality rate related to shockwave treatment is 0.5 per cent, which is surprisingly low considering the complexity of the problem and the population requiring treatment [72]. The mortality rate of adjuvant endoscopic or percutaneous procedures, which is about 1 per cent [61,64], must also be borne in mind [80]. For CBD stones that cannot be removed endoscopically, some authors feel that ESWT should be considered before surgery is undertaken, especially in the high-risk patient [76,80].

1.3 pancreatic duct stones

Chronic pancreatitis is often associated with calcification within the duct. Such stones may cause obstruction and the subsequent increased outflow pressure in the pancreatic duct is one pathogenic factor of persistent pain characterizing chronic pancreatitis [83]. When stones are present in the main pancreatic duct, sphincterotomy of the duct orifice followed by endoscopic stone extraction is the therapy of choice [84,85]. However, this is sometimes impossible and more troublesome than endoscopic extraction of CBD stones [85]. Extensive surgical procedures, such as side-to-side pancreatojejunostomy and left or main pancreatic resection, are often regarded as the only solution [86-88]. Unfortunately, these surgerical procedures are associated by a considerable morbidity and mortality rates of 20-40 and 2-5 per cent, respectively [89,90]. Shockwave treatment therefore seems an attractive alternative for the management of pancreatic duct stones that cannot be removed by endoscopic extraction.

The first report of successful extracorporeal shockwave therapy in a patient with chronic pancreatitis was published in 1987 [91]. Although pancreatic calculi are usually calcified,

non-calcified stones in the panceatic duct can also be treated by lithotripsy [92]. Apart from report on shockwave therapy in a large series of 123 patients [93], experience has usually been limited to fewer than 25 patients [83,92,94-98]. Fragmentation and stone clearance rates are good; all complications are clinically insignificant [99] (Table 1) .

Pain relief directly after treatment is observed in nearly all patients, but successful long-lasting pain relief occurs in 38 to 88 per cent of patients [83,92,94-98]. No associated death has been reported to date. Whether long-lasting pain relief can be achieved in these patients remains doubtful. In large series of patients operated on for chronic calcifying pancreatitis, long-lasting pain relief could not be achieved in 20-40 per cent [88-90,99-101]. Considering the moderate results of surgery and its attendant high morbidity and mortality rates, it is our opinion that lithotripsy should be the procedure of choice for treating pancreatic duct stones that cannot be removed endoscopically [92].

2. Salivary gland disease

Sialolithiasis is both a cause and consequence of chronic sialadenitis. In addition, salivary stones may produce acute suppurative sialadenitis. Parotidectomy is an accepted therapy for salivary gland stones, but it requires several hours of general anaesthesia and is associated with the risk of facial nerve palsy and Frey's syndrome. Removal of the submandibular gland may cause lesions of the lingual and hypoglossal nerves, and marginalis branch of the facial nerve.

Extracorporeal shockwave therapy for stones of the large salivary glands has been studied almost exclusively in Germany [102-106]. After initial in vitro studies [102], Iro and collegues treated the first patient in 1989 [103]. The results of a relatively large series of patients (n=51) appeared only recently [106]. Sixteen patients had stones in the parotid gland and 35 in the submandibular gland; fragmentation was achieved in 88 per cent. At 9-months follow-up total clearance of stone fragments was found in 53 per cent and 90 per cent of all patients were free from symptoms. Stone clearance was markedly more successful in the parotid gland than in the submandibular gland (81 vs. 40 per cent), probably because of anatomical and physiological differences between the two. Relief of symptoms was more pronounced after treatment of the parotid gland than of the submandibular gland (100 vs. 85 per cent) because of the difference in stone clearance rates. Most patients (71 per cent) required only one session of lithotripsy and no anaesthesia was required in any case. No

adjuvant treatment was required and no serious complications were observed (Table 1).

Although these data are promising, more patients and longer follow-up are warranted to determine the role of extracorporeal shockwave treatment in sialolithiasis. Because electromagnetic and electrohydraulic machines have substantially larger shockwave focal zones, possibly more likely to cause damage to surrounding tissues, shockwave treatment of salivary gland stones is likely to be practically possible only with piezoelectric lithotriptors [106].

3. Vascular disease

Extracorporeal shockwave therapy for vascular diseases has been studied experimentally for selective thrombus ablation and pretreatment of heavily calcified arteries.

Thrombosis of coronary and peripheral arteries is a major clinical problem, accompanied by large morbidity and mortality rates. Thrombolytic therapy has shortcomings in both eligibility and reperfusion rates. Alternatives are therefore being vigorously investigated. Because endovascular acoustic energy ablates thrombi with a wide margin of safety, the use of an external acoustic generator has been tested [107]. It was found that a significant ablation of thrombus mass could be achieved by shockwave treatment without microscopic damage to the arterial segments. Since there are no differences in impedance properties between thrombus mass and arterial wall, it has been suggested that thrombus ablation is caused solily by the cavitation effect. No in vivo experiments have been reported to date.

Atherosclerosis is another major clinical problem, often requiring open surgical or endovascular interventions. One serious difficulty in endovascular interventions is heavily calcified plaques in the artery; such lesions are the major cause of technical failure and complications of this type of intervention [108]. Occlusions may be treated by percutaneous ultrasonic angioplasty [109], but recently it has been postulated that shockwaves may be useful in the pretreatment of calcified arteries before balloon dilatation and atherectomy [110]. Early experimental results of this application of shockwaves are contradictory [110,111]. A research group in our hospital has demonstrated macroscopic and radiological decalcification using an electromagnetic shockwave generator on ex vivo segments of calcified abdominal aorta [110]. No perforations were observed nor was there histological evidence of significant damage to the non-calcified parts of the vessel. Contrary to these results, Cooke and Palfrey could not demonstrate any radiological effect in ex vivo calcified

vessels using a spark-gap lithotriptor [111]. No in vivo experimental results have been publised to date.

In summary, extracorporeal shockwave therapy for vascular disease remains experimental and its clinical use in the near future remains uncertain. One potentially serious difficulty is possible embolization in vivo caused by fragments of thrombi and calcified plaques.

4. Trauma

The treatment of fracture non-union is difficult and usually requires multiple surgical interventions. Extracorporeal shockwave therapy may become a non-invasive alternative treatment for these healing disturbances [112,113]. Shockwaves are known to be able to microfracture orthopaedic cement, resulting in a disruption of the cement-surface interface during the revision of total hip arthroplasty [114,115]. Shockwave therapy can also cause major gross cortical changes and even bone fracture in a dose-related manner [116]. Applied to fractured bone, shockwave treatment has shown a significant enhancement in radiological fracture healing and mechanical stability in a controlled experiment in rats [112]. In another experiment, dogs treated by shockwave therapy formed radiographically and histologically proven bony unions, while untreated dogs had persistent non-unions [117]. It was assumed that the stimulating influence of shockwaves on the healing processes of damaged tissues results from differences in shockwave susceptibility of different cell types [118]. Such a difference in shockwave susceptibility may lead to better growth by less shockwave-sensitive cells. These data suggest that extracorporeal shockwave therapy may have a role to play in the non-operative treatment of bone healing disturbances, such as pseudoarthrosis, delayed union and established non-union of fractures. Further studies are needed to define the full potential of this so-called osteotripsy. The first patients with bone healing disturbances are currently being treated [112,117].

5. Oncology

Because of the destructive effects of shockwaves on cells, extracorporeal shockwave therapy has also been studied in oncology, both as a sole treatment and as pretreatment before cytotoxic medication. Since there is no difference in viability after shockwave application between normal cells and tumour cells [119], the potential role for shockwave treatment as a non-ivasive antineoplastic technique must lie purely in its locally destructive effects. Russo

and co-workers were the first to report an inhibitory effect of shockwaves on the clonogenic potential of tumour cells in vitro and tumour growth in vivo [120-123]. A cytocidal and cytostatic effect was confirmed by several other authors using different shockwave generators on various tumour cell lines [124-130]. The potential ability of shockwave therapy to suppress tumour cell growth is, however, temporary [128].

The mechanism of action is not yet clear [131,132]. Most probably there is a direct mechanical effect on cell membrane structures [124,126], but is an oversimplification to consider the cytotoxic effect of shockwave treatment as purely mechanical [133]. Morgan et al. and Miller postulated that the destructive effect is enhanced by secondary processes [133,134]. The formation of free radicals caused by microcavitation might play an important role, but this has not yet been proved experimentally [133]. Further study is needed to characterize the lesion at the cellular level [124].

Although the majority of cells are killed by acoustic shockwaves over a range of frequencies, proliferation of the cells that remaine alive is not adversely influenced [135]. This observation is in agreement with reports that extracorporeal shockwave therapy reduces the size of tumours in vivo but does not alter the growth rate [128]. Such findings have led to the concept of combining shockwave treatment with cytotoxic drugs in the hope that the former will reduce the bulk of the tumour while the latter destroys residual tumour cells. Several studies have shown synergistic effects using such a combination [128,130,136-138]. The hypothesized mechanism of action of this synergetic effect is an increased membrane permeability after shockwave treatment [124].

Although the initial results of shockwave therapy in the treatment of tumours are encouraging, cautious interpretation is necessary [132,139]. A major drawback is that in vivo antitumour effects are less pronounced than those observed in vitro [128,130,136,137,139]. Some authors have suggested that the in vitro effects may have been influenced by experimental factors [132,134,135,139]. In fact, one cannot exclude that the cytotoxic effects observed in vitro might have been experimental artefacts.

In the oncological context, focused extracorporeal pyrotherapy must also be mentioned. Here, ultrashort focused waves are generated with the specific aim of destroying tumours by extracorporeal application. Although the pressure profiles of the ultrasonic waves differ from that of shockwaves, the generation of the former and their transmission through a water bag, closely resemble those of extracorporeal shockwave therapy. The lesion produced, however,

is different. In focused extracorporeal pyrotherapy, the waves cause a very brief period of great heat at the focal area. This ultrasonically induced tissue heating together with transient cavitation are the main cause of a direct coagulative necrosis [140]. These phenomena eventually lead to a decreased tumour growth rate, which has been observed in cultured tumour cells and implanted tumours in a variety of animals [141-144]. There seems to be no metastatic risk and skin burns are the only obvious side-effects of pyrotherapy [145]. Just as for shockwave treatment, pyrotherapy has also been tested as an adjuvant treatment with chemotherapy; a synergystic effect is suggested [146,147]. Focused extracorporeal pyrotherapy has already been investigated in humans with prostatic, kidney and bladder tumours and in benign disorders such as prostatic hyperplasia [145].

Most experiments in oncology suggest a potential value for extracorporeal shockwave treatment and focused extracorporeal pyrotherapy as non-invasive therapeutic tools for the destruction of malignant tumours in vivo. In contrast to radiotherapy, shockwave treatment and pyrotherapy have the advantage that waves can be brought to a sharp focus, causing fewer side-effects to exposed adjacent normal tissue [135]. Investigations into the possible use of extracorporeal shockwave treatment and focused extracorporeal pyrotherapy in conjunction with chemotherapy, radiotherapy and immunotherapy seem worthwile.

Conclusions

Extracorporeal shockwave therapy is mainly used in the treatment of stones, but other applications are being intensively investigated. In urology, shockwave therapy has revolutionized the treatment of kidney and urinary tract stones. Compared with lithotripsy of urological calculi, shockwave therapy of stones in other areas has not achieved the same high clearance rate, even after adjuvant treatment. Moreover, multiple treatment sessions are usually required. Most clinical experience of lithotripsy in general surgery has been gained in the field of hepatobiliary and pancreatic interventions. A major advantage of lithotripsy is that it can be performed under simple analgesic sedation; most treatments do not require anaesthesia at all. The method can therefore be offered to elderly and high-risk patients. Extracorporeal shockwave therapy may also be offered as an option to those who refuse surgery.

Since the successful introduction of laparoscopic cholecystectomy the role of shock wave treatment of gallbladder stones has been limited [148]. Lithotripsy for stones in the pancreatic

duct or CBD is an attractive alternative to surgery when they cannot be removed endoscopically. Considering the morbidity and mortality rates associated with surgery, it has been suggested that lithotripsy should be tried before operation is undertaken. While we agree that this strategy may be suitable for elderly and high-risk patients, it has not been studied in randomized controlled trials.

The initial results of lithotripsy for salivary stones are promising, but the number of patients treated is too limited to draw any firm conclusions on its future role. It is also premature to predict the role of extracorporeal shockwave therapy in vascular disease and oncology; no patients have been treated to date. Studies on shockwave treatment for selective thrombus ablation and pretreatment of heavily calcified arteries, however, are certainly interesting. The influence of shockwave treatment and pyrotherapy on the viabilty of malignant cells and growth rates of tumours also warrant further investigations. Finally, the initial results of extracorporeal shockwave therapy in the non-operative treatment of bone healing disturbances are encouraging and the first reports of clinical results are eagerly being awaited.

In summary, extracorporeal shockwave therapy has the potential to be an alternative to several surgical procedures. It must be stressed, however, that all such applications remain experimental. Shockwave therapy in vascular disease, trauma and oncology has almost exclusively been studied in an experimental setting. Lithotripsy for stones in the CBD and pancreatic duct has not yet been studied in randomized trials, and experience with shockwave treatment of salivary gland calculi is still very limited. Even extracorporeal shockwave therapy for gallstones may be regarded as still experimental; the American Food and Drug Administration has not yet approved lithotriptors for the treatment of gallstones to date [47], although already over 30,000 patients have already been treated worldwide [46].

References

1. Chaussy Ch, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980;ii:1265-8.
2. Chaussy CG, 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.
3. Brendel W. Shock waves: a new physical principle in medicine. Eur Surg Res 1986;18:177-80.
4. Ferruci JT. Biliary lithotripsy: 1989. AJR 1989;153:15-22.
5. Coleman AJ, Saunders JE, Crum LA, et al. Acoustic cavitation generated by an extracorporeal shockwave lithotriptor. Ultrasound Med Biol 1987;13:69-76.

6. Delius M, Brendel W, Heine G. A mechanism of gallstone destruction by extracorporeal shockwaves. Naturwissenschaften 1988;75:200-1.
7. Schneider HT, Ott R, Janowitz P, et al. In vitro fragmentation of gallstones: a comparison of three different shock wave principles. In: Paumgartner G, Sauerbruch T, Sackmann M, et al (eds): Lithotripsy and related techniques for gallstone treatment. Mosby Yearr Book, St. Louis, 1991.
8. Schneider HT, Fromm M, Ott R, et al. In vitro fragmentation of gallstones: comparison of electrohydraulic, electromagnetic and piezoelectric shockwave lithotripters. Hepatology 1991;14:301-5.
9. Schachler R, Bird NC, Sauerbruch T, et al. Extracorporeal shock wave lithotripsy of gallstones: an in vitro comparison between an electrohydraulic and a piezoeceramic device. Gut 1991;32:312-5.
10. Sass W, Steffen K, Matura E, et al. Experiences with lithotripters: measurements of standardized fragmentation. J Stone Dis 1992;4:129-40.
11. Barkun ANG, Ponchon T. Extracorporeal biliary lithotripsy: review of experimental studies and a clinical update. Ann Int Med 1990;112:126-37.
12. Vanderpool D, Jones RC, O'Leary JP, et al. Biliary lithotripsy. Am J Surg 1989;158:194-7.
13. Plaisier PW, Hul RL van der, Nijs HGT, et al. Eligibility for extracorporeal shock wave lithotripsy of gallbladder stones using different entry criteria. J Stone Dis 1993;5:125-30.
14. Simeone JT, Ferruci JT. New trends in gallstone imaging. JAMA 1981;246:380-3.
15. Sonnenberg E van, Hofmann AF. Horizons in gallstone therapy. AJR 1988;150:43-6.
16. Pixley F. Epidemiology. In: Bateson MC (ed). Gallstone disease and its management. Lancaster, PA:MTP Press, 1986.
17. Jörgenson T. Prevalence of gallstones in a Danish population. Am J Epidemiol 1987;126:12-21.
18. Thistle JL, Cleary PA, Lachin JM. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med 1984;101:171-5.
19. National Institutes of Health consensus development conference statement on gallstones and laparoscopic cholecystectomy. Am J Surg 1993;165:390-6.
20. Ransohoff DF, Gracie WA, Wolfensom LW. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 1983;99:199-204.
21. 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.
22. Finlayson N. Cholecystectomy for gallstones. A good thing if they cause symptoms. Br Med J 1989;298:133-4.
23. McSherry CK. Cholecystectomy: the gold standard. Am J Surg 1989;158:174-8.
24. McSherry CK, Glenn F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. Ann Surg 1980;191:271-5.
25. Gutman H, Kott I, Haddad M, et al. Changing trends in surgery for benign gallbladder disease. Am J Gastroenterol 1988;83:545-8.
26. Sauerbruch T, Delius M, Paumgartner G, et al. Fragmentation of gallstones by extracorporeal shock waves. N Eng J Med 1986;314:818-22.
27. 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.
28. Darzi A, El-Sayed E, O'Morain C, et al. Piezoelectric lithotripsy for gallstones: analysis of results in patients with extended selection. Br J Surg 1991;78: 163-6.
29. Zeman RK, Davros WJ, Goldberg JA, et al. Gallstone lithotripsy: results when number of stones is exlcuded as a criterion for treatment. AJR 1991;157;747-52.
30. Meiser G, Heinerman M, Lexer G, et al. Agressive extracorporeal shock wave lithotripsy of gall bladder stones within wider treatment criteria: fragmentation rate and early results. Gut 1992;33:277-81.
31. Toom R den, Vergunst H, Nijs HGT, et al. Electromagnetic lithotripsy of gallbladder stones: a wide range of inclusion criteria. Am J Gastroenterol 1992;87: 497-503.
32. Sackmann M, Pauletzki J, Delius M, et al. Noninvasive therapy of gallbladder calculi with a radiopaque rim. Gastroenterology 1992;102:988-93.
33. Rawat BR, Burenne HJ. Extracorporeal shock wave lithotripsy of calcified gallstones: work in progress. Radiology 1990;175:667-70.

34. Albert MB, Fromm H, Shenan CM. Densely calcified gallstone treated successfully with piezoelectric lithotripsy. Gastroenterology 1990;98:777-9.
35. Han JK, Choi BI, Yoon YB, et al. Piezoelectric lithotripsy of radiopaque gallstones: results and six months follow-up. J Stone Dis 1993;5:89-95.
36. Maher JW, Summers RW, Dean TR, et al. Early results of combined electrohydraulic shock-wave lithotripsy and oral litholytic therapy of gallbladder stones at the University of Ioha. Surgery 1990;108:648-54.
37. Ell C, Kerzel W, Schneider HT, et al. Piezoelectric lithotripsy: stone disintegration and follow-up results in patients with symptomatic gallbladder stones. Gastroenterology 1990;99:1439-44.
38. Fache JS, Rawat B, Burhenne HJ. Extracorporeal cholecystolithotripsy without oral chemolitholysis. Radiology 1990;177:719-21.
39. Classen M, Cremer M, Faustini S, et al. Electromagnetic shock-wave lithotripsy of gallbladder calculi. Multicentered preliminary report on experience with 276 patients. Hepatogastroenterol 1990;37:425-7.
40. Torres WE, Steinberg HV, Davis RC, et al. Extracorporeal shock wave lithotripsy of gallstones: results and 6-months follow-up in 141 patients. Radiology 1991:178:509-12.
41. Holl J, Suaerbruch T, Sackmann M, et al. Combined treatment of symptomatic gallbladder stones by extracorporeal shock-wave lithotripsy (ESWL) and methyl tert-butyl ether (MTBE). Dig Dis Sci 1991;36:1097-1101.
42. Sackmann M, Pauletzki J, Sauerbruch T, et al. The Munich gallbladder lithotripsy study: results of the first 711 patients. Ann Intern Med 1991;114: 290-6.
43. Erdamer I, Avci G, Füzün M, et al. Extracorporeal shockwave lithotripsy and litholytic therapy in cholelithiasis. Br J Surg 1992;79:235-6.
44. Elewaut A, Crape A, Afschrift M, et al. Results of extracorporeal shock wave lithotripsy of gall bladder stones in 693 patients: a plea for restriction to solitary radiolucent stones. Gut 1993;34:274-8.
45. Plaisier PW, Hul RL van der, Toom R den, et al. Gallstone lithotripsy: the Rotterdam experience. Hepatogastroenterol (in press).
46. Sauerbruch T, Holl J, Sackmann M, et al. Fragmentation of bile duct stones by extracorporeal shock-wave lithotripsy: a five-year experience. Hepatology 1992;15:208-14.
47. Nahrwold DL. Gallstone lithotripsy. Am J Surg 1993;165:431-4.
48. Sackmann M, Niller H, Ippisch E, et al. Gallstone recurrence after lithotripsy. Gastroenterology 1992;102:A332.
49. Rotschild JG, Holbrook RF, Reinhold RB. Gallstone lithotripsy vs cholecystectomy: a preliminary cost-benefit analysis. Arch Surg 1990;125:710-4.
50. Nealon WH, Urrutia F, Fleming D, et al. The economic burden of gallstone lithotripsy: will cost determine its fate? Ann Surg 1991;213:645-50.
51. Nicholl JP, Brazier JE, Milner PC, et al. Randomised controlled trial of costs-effectiveness of lithotripsy and open cholecystectomy as treatments for gallbladder stones. Lancet 1992;340:801-7.
52. Bass EB, Steinberg EP, Pitt HA, et al. Cost-effectiveness of extracorporeal shock-wave lithotripsy versus cholecystectomy for symptomatic gallstones. Gastroenterology 1991;101:189-99.
53. Schirmer BD, Edge SB, Dix J, et al. Laparoscopic cholecystectomy: treatment of choice for symptomatic cholelithiasis. Ann Surg 1991;213:665-77.
54. Macintyre IMC, Wilson RG. Laparoscopic cholecystectomy. Br J Surg 1993;80:552-9.
55. Fromm H. ESWL: A method on retreat? I. Extracorporeal shock-wave lithotripsy (ESWL) plays an important role in the treatment of gallbladder stones. Endoscopy 1992;24:271-2.
56. Plaisier PW, Hul RL van der, Nijs HGT, et al. The course of biliary and gastro-intestinal symptoms after gallstone therapy: results of a randomised study comparing extracorporeal shock wave lithotripsy with cholecystectomy. Am J Gastroenterol (in press).
57. Barkun AN, Barkun JS, Sampalis JS, et al. A randomized clinical trial comparing gallbladder stone shock wave lithotripsy to laparoscopic cholecystectomy. Gastroenterology 1993;104:A2.
58. Plaisier PW, Hul RL van der, Nijs HGT, et al. Quality of life after gallstone therapy: results of a randomised study comparing extracorporeal shock wave lithotripsy with open cholecystectomy. Eur J Surg (in press).
59. Vellacott KD, Powell PH. Exploration of the common duct: a comparitive study. Br J Surg 1979;66: 389-91.

60. Doyle PJ, Ward-McQuaid JN, McEwen Smith A. The value of routine preoperative cholangiography - a report of 4,000 cholecystectomies. Br J Surg 1982;69:617-9.
61. Cotton PB. Endoscopic management of bile duct stones (apples and oranges). Gut 1984;25:587-97.
62. Johnson AG, Hosking SW. Appraisal of the management of bile duct stones. Br J Surg 1987;74:555-60.
63. Zimmon DS. Alternatives to cholecystectomy and common duct exploration. Am J Gastroenterol 1988;83:1272-3.
64. Lambert ME, Betts CD, Hill J, et al. Endoscopic sphincterotomy: the whole truth. Br J Surg 1991;78:473-6.
65. Sauerbruch T, Stern M, and the study group for shock-wave lithotripsy of bile duct stones. 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.
66. Staritz M, Rambow A, Grosse A, et al. Electromagnettically 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.
67. Toom R den, Nijs HGT, Blankenstein M van, et al. 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.
68. Gordon SJ, Stampfl DA, Grimm IS, et al. Successful shock-wave lithotripsy of bile duct stones using ultrasound guidance. Dig Dis Sci 1991;36:1102-9.
69. Lindström E, Borch K, Kullman EP, et al. Extracorporeal shock wave lithotripsy of bile duct stones: a single institution experience. Gut 1992;33:1416-20.
70. Taylor MC, Marshall JC, Fried LA, et al. Extracorporeal shock wave lithotripsy (ESWL) in the management of complex biliary tract stone disease. Ann Surg 1988;280:586-92.
71. Bland KI, Jones RS, Maher JW, et al. Extracorporeal shock-wave lithotripsy of bile duct calculi. An interim report of the Dornier U.S. bile duct lithotripsy prospective study. Ann Surg 1989;209:743-55.
72. Moody FG, Amerson JR, Berci G, et al. Lithotripsy for bile duct stones. Am J Surg 1989;158:241-7.
73. Ihse I, Borch K, Carlsson P, et al. Extracorporeal shock-wave lithotripsy of bile duct stones. Acta Chir Scand 1990;156:87-90.
74. Ponchon T, Martin X, Barkun A. Extracorporeal lithotripsy of bile duct stones using ultrasonography for stone localization. Gastroenterology 1990;98:726-32.
75. Eckhauser FE, Raper SE, Knol JA, et al. Extracorporeal lithotripsy: an important adjunct in the nonoperative management of retained or recurrent common bile duct stones. Arch Surg 1991;126:829-35.
76. Dobrilla G, Pretis G de, Felder M, et al. Extracorporeal shock wave lithotripsy in bile duct stones refractory to papillosphincterotomy. Eur J Gastroenterol Hepatol 1992;4:475-80.
77. Weber J, Adamek HE, Riemann JF. Extracorporeal piezoelectric lithotripsy for retained bile duct stones. Endoscopy 1992;24:239-43.
78. Nicholson DA, Martin DF, Tweedle DEF, et al. Management of common bile duct stones using a second-generation extracorporeal shockwave lithotriptor. Br J Surg 1992;79:811-4.
79. Moody FG. Lithotripsy in the treatment of biliary stones. Am J Surg 1993;165:479-82.
80. Hul RL van der, Plaisier PW, Blankenstein M van, et al. Extracorporeal shock wave lithotripsy of stones in the common bile duct in patients at increased operative risk. Eur J Surg (in press).
81. Benes J, Chmel J, Dufek V, et al. Extracorporeal shock-wave lithotripsy of the common bile duct stone with ultrasound localization. J Hepatol 1989;9:95-8.
82. Ell C. ESWL: A method on retreat? I. ESWL or ISWL for difficult bile duct stones. Endoscopy 1992;24:273-5.
83. Sauerbruch T, Holl J, Sackmann M, et al. Extracorporeal lithotripsy of pancreatic stones in patients with chronic pancreatitis and pain: a prospective follow up study. Gut 1992;33:969-72.
84. Schneider MU, Lux G. Floating pancreatic duct concrements: pain relief by endoscopic removal. Endoscopy 1985;17:8-10.
85. Huibregtse K, Schneider B, Vrij AA, et al. Endoscopic pancreatic drainage in chronic pancreatitis. Gastrointest Endosc 1988;34:9-15.
86. Puestow CB, Gillesby WJ. Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. Arch Surg 1958;76:898-906.

87. Way LW, Gadacz T, Goldman L. Surgical treatment of chronic pancreatitis. Am J Surg 1974;127:202-9.
88. Bradley EL. Long-term results of pancreatojejunostomy in patients with chronic pancreatitis. Am J Surg 1987;153:207-13.
89. Prinz RA, Greenlee HB. Pancreatic duct drainage in 100 patients with chronic pancreatitis. Ann Surg 1981;194:313-20.
90. Mannell A, Adson MA, McIlrath DC, et al. Surgical management of chronic pancreatitis: long-term results in 141 patients. Br J Surg 1988;75:467-72.
91. Sauerbruch T, Holl J, Sackmann M, et al. Disintegration of a pancreatic duct stone with extracorporeal shock waves in a patient with chronic pancreatitis. Endoscopy 1987;19:207-8.
92. Hul RL van der, Plaisier PW, Jeekel J, et al. Extracorporeal shock wave lithotripsy of pancreatic duct stones. Endoscopy (in press).
93. Delhaye M, Vandermeeren A, Baize M, et al. Extracorporeal shock-wave lithotripsy of pancreatic calculi. Gastroenterology 1992;102:610-20.
94. Soehendra N, Grimm H, Meyer HW, et al. Extrakorporale Stoßwellenlithotripsie bei chronischer pankreatitis. Dtsch Med Wschr 1989;114:1402-6.
95. Kerzel W, Ell C, Schneider T, et al. Extracorporeal piezoelectric shockwave lithotripsy of multiple pancreatic duct stones under ultrasonographic control. Endoscopy 1989;21:229-31.
96. Neuhaus H, Hagenmüller K, Brandstetter K, et al. Extrakorporale Stoßwellenlithotripsie von pankreassteinen. In: Henning H, Manegold BC, eds. Fortschritte der Gastro-enterologischen Endoskopie. Gräfelfing: Demeter Verlag, 1990:39-43.
97. Sauerbruch T, Holl J, Sackmann M, et al. Extracorporeal shock wave lithotripsy of pancreatic stones. Gut 1989;30:1406-11.
98. Toom R den, Nijs HGT, Blankenstein M van, et al. Extracorporeal shock wave lithotripsy of pancreatic stones. Am J Gastroentrol 1991;86:1033-6.
99. Neuhaus H. Fragmentation of pancreatic stones by extracorporeal shock wave lithotripsy. Endoscopy 1991;23:161-5.
100. Ihse I, Borch K, Larsson J. Chronic pancreatitis: results of operations for relief of pain. World J Surg 1990;14: 53-8.
101. Greenlee HB, Prinz RA, Aranha GV. Long-term results of side-to-side pancreaticojejunostomy. World J Surg 1990;14:70-6.
102. Iro H, Nitsche N, Meier J, et al. Piezoelectric shock wave lithotripsy of salivary gland stones: an in vitro feasibility study. J Lithotripsy & Stone Dis 1991;3:211-6.
103. Iro H, Nitsche N, Schneider T, et al. Extracorporeal shock wave lithotripsy of salivary gland stones. Lancet 1989;ii:115.
104. Iro H, Nitsche N, Waitz G, et al. Extracorporeal piezolectric shock wave lithotripsy of salivary gland stones: first clinical experiences. J Stone Dis 1992;4:8-12.
105. Iro H, Waitz G, Nitsche N, et al. Extracorporeal piezolectric shock-wave lithotripsy of salivary gland stones. Laryngoscope 1992;102:492-4.
106. Iro H, Schneider T, Födra C, et al. Shockwave lithotripsy of salivary duct stones. Lancet 1992;339:1333-6.
107. Rosenschein U, Yakubov SJ, Guberinich D, et al. Shock-wave thrombus ablation, a new method for noninvasive mechanical thrombolysis. Am J Cardiol 1992;70:1358-61.
108. Leon MB, Almagor Y, Bartorelli AL, et al. Fluorescense-guided laser-assisted balloon angioplasty in patients with femoreopopliteal occlusions. Circulation 1990;81:143-55.
109. Siegel RJ, Cumberland DC, Crew JR. Ultrasound recanalization of diseased arteries: from experimental studies to clinical application. Surg Clin N Am 1992;72:879-95.
110. Dijk LC van, Johannes EJ, Gend R van, et al. Extracorporeal shock waves as a pretreatment for balloon dilatation of heavily calcified arteries. Angiology 1993;44:30.
111. Cooke DAP, Palfrey ELH. Is extracorporeal shock wave lithotripsy safe in patients with calcific arterial disease. Eur J Vasc Surg 1989;3:363-5.
112. Haupt G, Haupt A, Ekkernkamp A, et al. Influence of shock waves on fracture healing. Urology 1992;39:529-32.
113. Johannes EJ, Kaulesar Sukul DMKS, Pierik EGJM, et al. Non- operative treatment of nonunions in bone with extracorporeal shock waves. Eur Surg Res 1992;24(suppl2): 24.

114. Karpman RR, Magee FP, Gruen TW, et al. Work-in-progress #1. The lithotriptor and its potential use in the revision of total hip arthroplasty. Orthop Rev 1987;16:38-42.
115. Weinstein JN, Oster DM, Park JB, et al. The effect of the extracorporeal shock wave lithotriptor on the bone-cement interface in dogs. Clin Orthop 1988:235:261-7.
116. Kaulesar Sukul DMKS, Johannes EJ, Pierik EGJM, et al. The effect of high energy shock waves on cortical bone: an in vitro study. J Surg Res 1993;54:46-51.
117. Kaulesar Sukul DMKS, Johannes EJ. Osteotripsy: the treatment of fracture healing disturbances with extracorporeally induced high energy shock waves. Eur Surg Res 1993;25(suppl1):97-8.
118. Johannes EJ, Kaulesar Sukul DMKS, Bijma AM. Effects of high energy shock waves on normal human fibroblasts and chondrocytes in suspension. Eur Surg Res 1993;25(suppl1):52.
119. Brümmer F, Suhr D, Hülser DF. Sensitivity of normal and malignant cells to shock waves. J Stone Dis 1992;4:243-8.
120. Russo P, Stephenson RA, Heston W, et al. The in vitro effect of high energy shock waves on human prostate cancer cell line PC-3. Cancer Res 1985;26:267.
121. Russo P, Stephenson R, Heston WDW, et al. The effect of extracorporeal shock waves on Dunning R3327 AT-3 prostatic carcinoma. J Urol 1985;133:124A.
122. Stephenson RA, Russo P, Gay H, et al. The effect of extracorporeal shock waves on flow cytometric parameters in the Dunning R3327 AT-3 rat prostate tumor. J Urol 1985;133:371A.
123. 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.
124. Chaussy CG, Randazzo RF, Fuchs GJ. The effects of extracorporeal shock waves on Fanft bladder tumors in C3/He mice. J Urol 1986;135:289A.
125. Randazzo RF, Chaussy CG, Fuchs GJ, et al. The in vitro and in vivo effects of extracorporeal shock waves on malignant cells. Urol Res 1988;16:419-26.
126. Berens ME, Schostock C, Hart L, et al. Effect of cell cycle and temperature on the antiproliferative effect of acoustic shockwaves (SW) against human tumor cells. J Urol 1988;139:304A.
127. Dongen JW van, Steenbrugge GJ van, Romijn JC, et al. The cytocidal effect of high energy shock waves on human prostatic tumour cell lines. Eur J Cancer Clin Oncol 1989;25:1173-9.
128. Oosterhof GON, Smits GAHJ, Ruyter AE de, et al. The in vitro effect of electromagnettically generated shock waves (Lithostar) on the Dunning R3327 PAT-2 rat prostatic cancer cell line: a potentiating effect on the in vitro cytotoxicity of vinblastin. Urol Res 1989;17:13-9.
129. Berens ME, Welander CE, Griffin AS, et al. Effect of acoustic shock waves on clonogenic growth and drug sensitivity of human tumor cells in vitro. J Urol 1989;142:1090-4.
130. Oosterhof GON, Smits GAHJ, Ruyter AE de, et al. In vivo effects of high energy shock waves on urological tumors: an evaluation of treatment modalities. J Urol 1990;144:785-9.
131. Russo P, Mies C, Huryk R, et al. Histopathologic and ultrastructural correlates of tumor growth suppression by high energy shock waves. J Urol 1987;137:338-41.
132. Smits G, Oosterhof G, Ruyter A de, et al. Cytotoxic effects of high-energy shock waves in different in vitro models: influence of the experimental set-up. J Urol 1991;145:171-5.
133. Morgan TR, Laudone VP, Heston WDW, et al. Free radical production by high energy shock waves-comparison with ionizing radiation. J Urol 1988;139:186-9.
134. Miller DL. A review of the ultrasonic bioeffects of microsonation, gas-body activation, and related cavitation-like phenomena. Ultrasound Med Biol 1987;13:443-70.
135. Jones BJ, McHale AP, Butler MR. Effect of high-energy shock wave frequency on viability of malignant cell lines in vitro. Eur Urol 1992;22:70-3.
136. Lee K, O'Donnell RW, Smith P, et al. High-energy shock waves enhance antitumor activity of cis-platinum (DDP) in murine bladder cancer MBT-2. J Urol 1988;139:326A.
137. Lee K, Smith P, Cockett ATC. Influence of high-energy shock waves enhance antitumor activity of cis-platin on antitumor effects in murine bladder cancer. Urol 1990;36:440-4.
138. Gambihler S, Delius M. In vitro interaction of lithotriptor shock waves and cytotoxic drugs. Br J Cancer 1992;66:69-73.
139. Laudone VP, Morgan TR, Huryk RF, et al. Cytotoxicity of high energy shock waves in different in vitro models: methodologic considerations. J Urol 1989;141:965-8.
140. Chen L, Rivens I, Haar ter G, et al. Histological changes in rat liver tumours tretaed with high-intensity focused ultrasound. Ultrasound Med Biol 1993;19:66-74.

141. Haar G ter, Sinnet D, Rivens I. High intensity focused ultrasound- a surgical technique for the treatment of discrete liver tumours. Phys Med Biol 1989;24:1743-50.
142. Haar G ter, Rivens I, Chen L, et al. High intensity focused ultrasound for the treatment of rat tumours. Phys Med Biol 1991;36:1495-501.
143. Vallancien G, Chartier-Kastler E, Chopin D, et al. Focussed extracorporeal pyrotherapy: experimental results. Eur Urol 1991;20:211-9.
144. Chartier-Kastler E, Chopin D, Vallancien G. The effects of focused extracorporeal pyrotherapy on a human bladder tumor cell line (647 V). J Urol 1993;149:643-7.
145. Vallancien G, Chartier-Kastler E, Bataille N, et al. Focused extracorporeal pyrotherapy. Eur Urol 1993;23(suppl 1):48-52.
146. Moore WE, Lopez RM, Mattews DE, et al. Evaluation of high-intensity therapeutic ultrasound irradiation in the treatment of experimental hepatoma. J Pedr Surg 1989;24:30-3.
147. Loverock P, Haar ter G, Ormerod MG, et al. The effect of ultrasound on the cytotoxicity of adriamycin. Br J Radiol 1990;63:542-6.
148. Plaisier PW, Hul RL van der, Terpstra OT, et al. Current treatment modalities for symptomatic gallstones. Am J Gastroenterol 1993;88:633-9.

Table 1 : results of lithotripsy of different stones

	Gallbladder stones	CBD stones	Pancreatic duct stones	Salivary gland stones
Fragmentation rates (%)	95-100	81-97	75-100	88
Stone clearance rates (%)	30-78	70-88[1]	38-100	53
Side effects (%)	-colics (14-54) -cholecystitis (1-4) -biliary obstruction/ pancreatitis (0-4)	-hematuria (2-11) -hemobilia (2-8) -septic fever (3-6)	-exacerbation pancreatitis (8-13)	-skin petechia (14) -transient gland swelling (3)
References	13, 26-32, 35-45, 47, 51	26, 46, 65-67, 69-73, 75, 76, 78-81	83, 92-94, 96-99	106

CBD = common bile duct

1) Ponchon [74] and Ihse [73] reported framentation rates of 53 and 67%, respectively.; since their protocols differred strikingly from most other reports, their data were excluded.

CHAPTER 12

Summary and discussion

The objective of this study was to determine the role of extracorporeal shock wave lithotripsy (ESWL) in the spectrum of treatment modalities for symptomatic gallstones in terms of in terms of eligibilty, stone clearance, safety, symptom relief, general well being and cost-effectiveness. The factors influencing the public's interest in the study were also studied. Laparoscopic cholecystectomy was incorporated in the study, because of its universal adoption as the new gold standard for symptomatic gallstones. Finally, the potential value of extracorporeal shock waves in fields other than gallbladder stones was investigated.

Chapter 2 reviews the literature on the currently available treatment modalities for symptomatic gallstones. In historical order, open cholecystectomy, oral bile acid therapy, contact dissolution, ESWL, cholecystolithotomy, rotary contact lithotripsy and laparoscopic cholecystectomy are discussed in detail. Cholecystectomy is the most rational treatment for symptomatic gallstones. First, because cholecystectomy is applicable in most patients, and second, because there is no possibility of stone recurrence. The limited role of nonoperative alternatives seems determined by their limited applicability, their limited efficacy, the necessity for a more extended diagnostic work-up and stone recurrence. Laparoscopic cholecystectomy will be the new gold standard for symptomatic gallstones. Alternative treatment modalities may be reserved for patients with a high surgical risk and for patients, who refuse surgery.

Chapter 3 reports on our calculations on the eligibility for ESWL using different entry criteria. It was found that only a small part of the symptomatic gallstone patients is eligible for ESWL: 13.4-46.9%, depending on the entry criteria used. Ideal patients (with a solitary non-calcified gallstone of $\leq$20mm) were found in only 10.3%. When the overall results of ESWL were compared with eligibility, there was no inverse relationship. This suggests that patient selection is not the only important factor determining the results of therapy. Other factors, such as treatment schemes, the lithotriptors used and experience of the treating physicians, may also play an important role in the outcome of ESWL therapy.

Chapter 4 presents our results of gallstone lithotripsy in 133 patients. At 1 year after the first ESWL-session, 51.0% of the patients with a solitary stone and 8.3% of the patients with 2-10 stones were free of concrements. Major complications comprised pancreatitis (3.0%)

and acute cholecystitis (0.8%). At final follow-up (mean: 17.7 months), 27.8% of the patients were free of stones and 22.6% underwent cholecystectomy. Fourteen per cent of the patients developed recurrent stones. Our results reconfirmed that ESWL is relatively safe and moderately effective in selected patients. Considering the poor results in multiple stones, ESWL should be confined to solitary stones.

Chapter 5 describes the course of biliary and gastrointestinal symptoms in 23 patients randomized to ESWL and 26 patients randomized to conventional cholecystectomy. Biliary colics were cured in 90.9% and 45.4% of the patients within 3 months after cholecystectomy or ESWL, respectively. Stomach swelling and fatty food upset responded to cholecystectomy, while nausea reponded to ESWL. Vomiting, pyrosis, ructus, diarrhea and constipation did not respond to gallstone therapy. Cholecystectomy is, therefore, superior to ESWL in improving biliary and gastrointestinal complaints. However, in patients who are unfit or unwilling to undergo surgery, ESWL is a relatively adequate therapy because the majority of patients tend to benefit from it in terms of symptom relief.

Chapter 6 deals with the course of quality of life after ESWL in comparison with open cholecystectomy in the same patient group as described in Chapter 5. Both treatment modalities were found to improve quality of life. Open cholecystectomy, however, improved quality of life significantly better than ESWL during the course of one year. Open cholecystectomy is, therefore, superior to ESWL in improving quality of life and remains the therapy of choice for symptomatic gallstones. However, in patients who are unfit or unwilling to undergo surgery, ESWL is an adequate form of treatment because the majority of patients tend to benefit from it in terms of quality of life.

Chapter 7 focuses on cost-effectiveness of ESWL in comparison with cholecystectomy. The results of our own cost-effectiveness analysis as well as the data in the literature indicate that ESWL is not as cost-effective as cholecystectomy. Cholecystectomy is, therefore, from an economic point of view, preferable to ESWL, except perhaps for elderly patients with solitary stones.

Chapter 8 reports on the findings at oral cholecystography (OCG) and its implications for

nonsurgical therapy of symptomatic gallstones. Age was found to be a determinant for calcification of gallstones. Elderly patients, in whom nonsurgical treatment of gallbladder stones is most likely to be indicated, are, therefore, less likely to be suitable for nonsurgical gallstone therapy.

Chapter 9 analyses patient accrual into our randomized study comparing ESWL with open cholecystectomy. It was found that in a 3-years intake period, only 8.3% of the analyzed patients could be entered into the trial. Three factors were identified hampering patient accrual. First, restricted eligibility for ESWL (and thus for the study), which could not have been predicted on the data provided in the literature. Second, the introduction of laparoscopic cholecystectomy. And third, strong patient's preference for a certain treatment modality for gallstone disease, inhibiting randomization. It is concluded that it is not always feasible to conduct a randomized study in surgery satisfactory due to unforseen circumstances. Because the management of gallstone disease is quickly evolving and because the characteristics of the different treatment modalities are so very divergent, a good randomized controlled study of laparoscopic cholecystectomy can most probably never be performed.

Chapter 10 investigates quality of life and the course of biliary and gastrointestinal symptoms afer laparoscopic cholecystectomy and conventional cholecystectomy. Quality of life significantly improved 6 months after laparoscopic cholecystectomy and to a similar degree 12 months after conventional cholecystectomy. Stomach swelling, fatty food upset and nausea improved significantly after cholecystectomy but sooner after laparoscopic than after conventional cholecystectomy. Vomiting and belching had a tendency to improve slightly, while pyrosis, constipation and diarrhea did not improve. Biliary pain was cured in 81% of the patients directly after cholecystectomy and not reported after 6 months after treatment. It is concluded that cholecystectomy improves quality of life and cures nausea, fatty food upset, stomach swelling and biliary pain. Furthermore, laparoscopic cholecystectomy improves quality of life and symptomatology to the same degree in an earlier stage than conventional cholecystectomy. Therefore, laparoscopic cholecystectomy may be preferable to conventional cholecystectomy for the treatment of uncomplicated symptomatic gallstones.

Chapter 11 discusses the potential applications of extracorporeal shock waves in surgery. Lithotripsy of stones in the gallbladder, common bile duct, pancreatic duct and salivary gland ducts are described. Steps towards the management of bone healing disturbances, the inhibition of tumor growth, selective thrombus ablation and pretreatment of heavily calcified arteries are discussed. Results indicate that for selected patients, extracorporeal shock wave therapy may serve as a useful addition to the surgical armamentarium.

Much research is being performed on the various aspects of the different treatment modalities for symptomatic gallstone disease. This research is in full development and major advances have been made. Therefore, it is somewhat disturbing that laparoscopic cholecystectomy could have emerged as the new standard therapy for symptomatic gallstones despite that a solid scientific basis for this unanimous acceptance, in fact, fails.

We studied ESWL to determine its role in the whole spectrum of treatment modalities for symptomatic gallstones. We found that ESWL may not be regarded as the therapy of choice for symptomatic gallstones. It is only applicable in a minority of patients and the efficacy is relatively poor, especially when multiple stones are treated. As compared to cholecystectomy, ESWL is not as effective in improving biliary pain, gastrointestinal symptoms and quality of life. Finally, ESWL is accompanied by stone recurrence and considerable costs.

Although ESWL did not come up to the high expectations, ESWL may still play a role for it is relatively safe and tends to improve quality of life and biliary pain. ESWL is especially indicated in elderly, high-risk patients. Considering that patient's preference is becoming increasingly important there should also be place for gallstone lithotripsy for patients who refuse surgery. For the latter group, it might be argued that only solitary stones should be treated. The results of other applications of extracorporeal shock waves in surgery are promising.

Het primaire doel van de in dit proefschrift beschreven studie was te onderzoeken welke rol galsteenvergruizing zou kunnen spelen in het arsenaal van galsteentherapieën. Het onderzoek richtte zich in het bijzonder op de intrinsieke eigenschappen van ESWL, zoals toepasbaarheid, steenklaring, veiligheid, de invloed op biliaire- en gastrointestinale symptomen, de invloed op het algemeen welbevinden van de patiënt en kosten-effectiviteit. Factoren die de interesse van het publiek in de studie beïnvloeden werden ook bestudeerd. De laparoscopische cholecystectomie werd in de studie opgenomen vanwege het feit dat deze ingreep inmiddels wereldwijd wordt gezien als de voorkeursbehandeling voor symptomatische galstenen. Tenslotte werden de mogelijke andere toepassingen van schokgolven bestudeerd.

Hoofdstuk 2 geeft een algemeen overzicht van de thans beschikbare therapievormen voor symptomatische galstenen. In historische volgorde worden achtereenvolgens behandeld de open (inmiddels 'klassieke') cholecystectomie, galzuur-therapie, contact-dissolutie, schokgolfvergruizing, cholecystolithotomie, 'rotary contact lithotripsy' en laparoscopische cholecystectomie. Extirpatie van de galblaas is de meest rationele behandeling voor symptomatische galstenen. Allereerst, is cholecystectomie toepasbaar in vrijwel alle patiënten en ten tweede is er na verwijdering van de galblaas geen kans op recidief-steenvorming. De rol van niet-operatieve behandelmethoden lijkt beperkt. Dit wordt veroorzaakt doordat niet-operatieve behandelvormen gepaard gaan met een beperkte toepasbaarheid, een beperkte effectiviteit, de noodzaak voor een meer uitgebreide diagnostische screening en de kans op recidief-steenvorming. Op basis van de beschikbare literatuur kan worden geconcludeerd dat de laparoscopische cholecystectomie de nieuwe gouden standaard is voor symptomatische galstenen. Niet-operatieve behandelmethoden zullen gereserveerd zijn voor patiënten met een hoog operatie-risico of patiënten, die geen operatieve ingreep wensen te ondergaan.

Hoofdstuk 3 geeft de toepasbaarheid van ESWL weer, zoals die werd berekend voor de verschillende insluitcriteria. Slechts de minderheid van de patiënten blijkt voor vergruizing van hun galstenen in aanmerking te komen: 13.4-46.9% afhankelijk van de gehanteerde insluitcriteria. Slechts 10.3% van de patiënten kunnen als 'ideale' vergruizingskandidaten worden bestempeld. 'Ideaal' wil in deze context zeggen maximaal één niet-gecalcificeerde steen met een maximale diameter van maximaal 20mm. Wanneer de resultaten van ESWL worden afgezet tegen de berekende toepasbaarheid, blijkt er geen omgekeerde relatie te

bestaan. Dit suggereert dat selectie van patiënten níet de enige belangrijke factor kan zijn die de resultaten van de behandeling bepaalt. Andere factoren, zoals behandelprotocollen, de soort vergruizer en de ervaring van de behandelaar moeten een belangrijke rol spelen in het uiteindelijke resultaat van de vergruizing.

In **Hoofdstuk 4** worden de Rotterdamse resultaten gepresenteerd van de verguizingen bij 133 galsteenpatiënten. Na 1 jaar blijken respectievelijk 51.0% van de patiënten met een solitaire steen en 8.3% van de patiënten met 2-10 stenen vrij van concrementen te zijn. Ernstige complicaties bestaan uit pancreatitis (3.0%) en acute cholecystitis (0.8%). Tijdens de laatste follow-up met een gemiddeld duur van 17.7 maanden, is 27.8% van de patiënten steenvrij en 22.6% heeft alsnog cholecystectomie ondergaan. Veertien procent van de patiënten ontwikkelt recidief-galstenen. Deze resultaten bevestigen dat ESWL veilig is en relatief effectief voor geselecteerd patiënten. Gezien de magere resulaten bij multipele stenen, dient ESWL slechts te worden toegepast bij patiënten met solitaire stenen.

Hoofdstuk 5 beschrijft het verloop van biliaire en gastrointestinale klachten bij 23 patiënten gerandomiseerd voor ESWL en 26 patiënten gerandomiseerd voor klassieke cholecystectomie. Binnen drie maanden na de behandeling genezen kolieken bij 90.9% van de cholecystectomie-patiënten en 45.4% van de ESWL-patiënten. Opgeblazen gevoel en vet-intolerantie reageren op cholecystectomie, terwijl misselijkheid afneemt na ESWL. Braken, zuurbranden, opboeren, diarree en obstipatie reageren niet op galsteenbehandeling. Cholecystectomie is derhalve superieur aan ESWL voor de behandeling van kolieken en gastrointestinale klachten. Echter voor patiënten met een hoog operatie-risico en patiënten die operatie afwijzen, kan ESWL een relatief adequate therapie zijn, omdat biliare en gastrointestinale als regel klachten afnemen.

In **Hoofdstuk 6** wordt de invloed van therapie op het verloop van het algemeen welbevinden van galsteenpatiënten behandeld. Dit algemeen welbevinden of 'kwaliteit van leven' werd bepaald in dezelfde patiëntengroepen als beschreven in Hoofdstuk 5. Zowel ESWL als cholecystectomie verbeteren het algemeen welbevinden van galsteenpatiënten. Echter de klassieke cholecystectomie verbetert de kwaliteit van leven significant beter. Cholecystectomie is daarom superieur aan ESWL en moet als gouden standaard beschouwd

blijven voor de behandeling van symptomatische galstenen. Voor patiënten met een hoog operatie-risico en patiënten die operatie afwijzen moet ESWL gezien worden als een adequate behandelvorm daar het het algemeen welbevinden duidelijk verbetert.

In **Hoofdstuk 7** wordt ingegaan op de kosten-effectiviteit van ESWL in vergelijking met die van cholecystectomie. Zowel onze eigen analyse als de literatuurgegevens gegeven aan dat ESWL niet zo kosten-effectief is als cholecystectomie. Vanuit economisch oogpunt is cholecystectomie derhalve te preferen boven ESWL. Een uitzondering hierop vormen wellicht oudere patiënten met solitaire stenen.

Hoofdstuk 8 geeft een analyse van de bevindingen bij de orale cholecystografieën van 448 symptomatische galsteenpatiënten en de implicaties hiervan voor niet-operatieve behandelvormen van galstenen. Leeftijd blijkt te predisponeren voor het hebben van verkalkte galstenen. Oudere patiënten komen daarom minder in aanmerking voor niet-operatieve behandelvormen van galstenen.

Hoofdstuk 9 analyseert de instroom van patiënten in het gerandomiseerde gedeelte van de ROGAL-studie. In een intake-periode van drie jaar konden slechts 8.3% van de geanalyseerde patiënten worden gerandomiseerd. Drie factoren blijken verantwoordelijk te zijn geweest voor deze matige patiënten-instroom. Allereerst de beperkte toepasbaarheid van ESWL. Een beperking, overigens, die niet kon worden voorspeld op basis van de destijds beschikbare literatuurgegevens. Ten tweede de introductie van de laparoscopische cholecystectomie. En ten derde de -tijdens de studie wisselende- uitdrukkelijke voorkeur voor een bepaalde behandelmethode van de zijde van de patiënt. Er wordt geconcludeerd dat het binnen de chirurgie door onvoorziene omstandigheden niet altijd mogelijk is een gerandomiseerde studie naar tevredenheid uit te voeren. Omdat ontwikkelingen binnen het gebied van de verschillende behandelvormen zich snel opvolgen en omdat de karakteristieken van de diverse behandelvormen zo uiteenlopen, zal een goede gerandomiseerde studie met de laparoscopische cholecystectomie waarschijnlijk onuitvoerbaar zijn.

Hoofdstuk 10 gaat in op het algemeen welbevinden en het verloop van biliaire en gastrointestinale klachten na laparoscopische en klassieke cholecystectomie. Zes maanden na

laparoscopische cholecystectomie en twaalf maanden na klassieke cholecystectomie verbetert de kwaliteit van leven significant. Opgeblazen gevoel, vet-intolerantie en misselijkheid reageren op cholecystectomie, maar beduidend sneller op laparoscopische dan op klassieke cholecystectomie. Braken en opboeren lijken wat te verbeteren, terwijl zuurbranden, obstipatie en diarree niet reageren. Biliaire pijn geneest in 81% van de gevallen aansluitend op cholecystectomie en wordt niet meer gerapporteerd na 6 maanden. Er wordt geconcludeerd dat cholecystectomie het algemeen welbevinden verbetert en misselijkheid, vet-intolerantie, opgeblazen gevoel en kolieken geneest. Laparoscopische cholecystectomie verbetert de kwaliteit van leven en diverse biliaire en gastrointestinale klachten sneller dan klassieke cholecystectomie. Laparoscopische cholecystectomie is daarom te prefereren.

Hoofdstuk 11 geeft een overzicht van de mogelijke andere toepassingen van schokgolven binnen de chirurgie. Vergruizing van stenen in de galblaas, galwegen, alvleesklier en speekselklieren worden besproken. Ook wordt ingegaan op mogelijkheden voor de behandeling van stoornissen in de botgenezing, de inhibitie van tumorgroei, selectieve thrombusverwijdering en de voorbehandeling van sterk verkalkte bloedvaten. De resultaten geven aan dat het gebruik van schokgolven van waarde is binnen het geheel van chirurgische behandeltechnieken.

Onderzoek naar de verschillende aspecten van de diverse behandelvormen van galstenen mag zich verheugen in een brede belangstelling. Dit onderzoek is nog steeds in volle ontwikkeling en belangrijke vooruitgangen zijn geboekt de laatste jaren. Het is daarom verontrustend dat de laparoscopische cholecystectomie kon verworden tot therapie van voorkeur, terwijl hiervoor, in feite, een solide wetenschappelijke basis ontbreekt.

Wij bestudeerden galsteenvergruizing om tot een plaatsbepaling van deze nieuwe techniek te komen binnen het spectrum van behandelmethoden voor symptomatische galstenen. We vonden dat ESWL niet mag worden beschouwd als de voorkeursbehandeling van symptomatische galstenen. Galsteenvergruizing is beperkt toepasbaar en de resultaten zijn matig, zeker wanneer multipele stenen worden behandeld. Vergeleken met cholecystectomie, is ESWL is niet zo effectief ten aanzien van het verbeteren van kolieken, gastrointestinale

klachten en het algemeen welbevinden. Tenslotte gaat ESWL gepaard met aanzienlijke kosten en recidief-steenvorming.

Hoewel galsteenvergruizing niet aan de hooggespannen verwachtingen heeft kunnen voldoen, kan toch gesteld worden dat ESWL relatief veilig is, het algemeen welbevinden verbetert en de frequentie van galsteenkolieken doet afnemen. Er is daarom toch een rol voor galsteenvergruizing weggelegd en wel speciaal voor oudere patiënten met een hoog operatie-risico. Gezien het feit dat de voorkeuren van patiënten steeds een steeds belangrijker rol gaan spelen, is er ook een plaats voor ESWL voor patiënten die operatie afwijzen. Voor deze groep zou kunnen worden gesteld dat zie hiervoor alleen in aanmerking mogen komen wanneer zij een solitaire galsteen hebben. De resultaten van andere toepassingen van schokgolven binnen de chirurgie zijn hoopgevend.

Dankwoord

Velen hebben bijgedragen aan de uiteindelijke voltooiing van dit proefschrift. Allen ben ik daarvoor zeer erkentelijk. Mijn speciale dank gaat uit naar:

-mijn promotores, Prof. Dr H.A. Bruining en Prof. Dr O.T. Terpstra, voor het in mij gestelde vertrouwen en hun voortreffelijke supervisie op zowel wetenschappelijk als klinisch gebied.

-de leden van het ROGAL-team, Dr(s) R.L. van der Hul, Dr H.G.T. Nijs, Dr R. den Toom, Dr K. Brakel en Dr H. Vergunst, voor de prettige samenwerking.

-alle co-auteurs voor hun snelle commentaar en waardevolle suggesties.

-de leden van de promotie-commissie, Dr J.S. Laméris en Prof. Dr S.W. Schalm, voor het beoordelen van het manuscript.

-Prof. Dr H. Obertop, Prof. Dr G.P. van Berge Henegouwen en Dr H.G.T. Nijs voor hun bereidheid de oppositie te willen voeren tijdens de promotie.

-de (tijdelijke) bewoners van kamer H903, René, Lukas, Ietje en Marga, voor de gezelligheid. René, het samen afsluiten van het project met een promotie vind ik een voorrecht en past perfect in onze pathologisch-symbiotische relatie. Marga, de galsteen-poli was mede dankzij jou altijd een feest; je hulp bij het vervaardigen, vermenigvuldigen en versturen van de manuscripten onmisbaar.

-de collegae Dr R.K.J. Koumans, Dr M.B. Lagaay, Drs R. Koelemij, Dr O.C.M. Varin, Dr K.G.Tan, Dr J. de Gruyl en Drs A.B. Rottier voor hun inspanningen de trial te redden.

-Matty van Rossen voor de assistentie (of eigenlijk: supervisie) bij de vergruizingen.

-'onze' paranimfen Roelf Postema, Carlos Quero, Lukas van Dijk en Hajo Auwerda voor hun vriendschap en voor hun bereidheid op 30 maart René en mij bij te staan.

-mijn ouders voor hun vertrouwen en hun morele en financiële steun; het proefschrift is zeker niet pro forma aan hen opgedragen.

-'zusje' voor de gouden tip.

-mijn allerliefste Ieneke, tot slot, voor je steun, je vriendschap en niet in de laatste plaats voor je gewillig oor voor de perikelen rond stukjes, boekje en opleiding.

Curriculum vitae

De auteur van dit proefschrift werd geboren op 23 oktober 1965 in Rotterdam. De middelbare school-opleiding (VWO) werd gevolgd aan de Christelijke scholengemeenschap Melanchthon te Rotterdam. In september 1984 werd de medische studie begonnen aan de Erasmus Universiteit Rotterdam. Na het behalen van het doctoraal examen in juli 1988 werd voor de periode van een jaar gewerkt als student-assistent in het Laboratorium Inwendige Geneeskunde III van het Academisch Ziekenhuis Dijkzigt (supervisie: Prof. Dr G. Hennemann). Het artsexamen werd behaald in maart 1991. In de periode van april 1991 tot juli 1993 werd in het kader van de "Rotterdam Gallstone Study-ROGAL" gewerkt aan dit proefschrift (supervisie: Prof. Dr O.T. Terpstra en Prof. Dr H.A. Bruining). Van juli tot en met december 1993 werd gewerkt als arts-assistent (AGNIO) op de afdeling Algemene Heelkunde van het Academisch Ziekenhuis Dijkzigt (hoofd: Prof. Dr J. Jeekel). Op dezelfde afdeling werd per 1 januari 1994 de opleiding tot algemeen chirurg aangevangen (opleider: Prof. Dr H.A. Bruining).