

REVIEW

Extracorporeal shock wave lithotripsy of gallstones revisited: Current status and future promises

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Abstract The improvement and refinement of extracorporeal shock wave lithotripsy (ESWL) has made this non-invasive treatment modality not only more effective, but also applicable to a larger population of gallstone patients. It can be performed safely on an outpatient basis. Advances in lithotripsy technology have made it possible to fragment stones into very small, sand-like particles (pulverization), which clear the gall-bladder faster than large fragments. Recent studies provide evidence that adjuvant bile acids may not be necessary in most cases in which pulverization is achieved. Good gall-bladder emptying appears both to promote the clearance of gallstones after ESWL and to decrease their recurrence. Although generally found to be more expensive than surgery if bile acids are used, ESWL should be cost-effective, as bile acids may not be necessary in all patients. Elderly patients with radiolucent, solitary and less than 30 mm gallstones can particularly benefit from lithotripsy.

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INTRODUCTION

As one of the commonest medical conditions in the Western world, gallstones represent the most frequent hepatobiliary cause for hospital admissions in the United States and Europe. The prevalence of gallstones increases with age. At the age of 60, approximately one-fifth of the population has gallstones, the majority of which are asymptomatic. Asymptomatic gallstones do not warrant any intervention, with the exception of certain scenarios where prophylactic cholecystectomy has been shown to be beneficial, as, for example, in sickle cell disease. Most symptomatic gallstones, especially those associated with complications, are best managed surgically. However, many times, a cholecystectomy is performed in spite of the absence of biliary pain; that is, patients are operated for symptoms that are either non-specific (i.e. dyspepsia, irritable bowel syndrome etc.) or related to conditions other than gallstones, such as peptic ulcer disease and inflammatory bowel disease. In the last decade, new non-surgical modalities have been used to treat gallstones, such as extracorporeal shock wave lithotripsy (ESWL),

oral dissolution treatment with bile acids, and topical gallstone dissolution with methyl *tert*-butyl ether. Although laparoscopic cholecystectomy (LC) has markedly decreased the enthusiasm for non-surgical treatment of gallstones, several recent developments and findings warrant a re-evaluation of the current role of medical treatment in the management of gallstones. First, not unexpectedly, LC is associated with significant complications. Both the rate and severity of bile duct injuries are higher with LC than the conventional open cholecystectomy (CC).¹ Second, LC has not brought the desired cost saving, as the number of cholecystectomies performed has increased considerably with the use of this new operative method. Finally, and perhaps most significantly, with further improvement and refinement of lithotripsy techniques, ESWL has become not only more effective, but also applicable to a larger patient population. The aim of this article is to provide an update on the role of medical treatment in the management of gallstones with emphasis on the comparative cost-effectiveness, mortality and morbidity of ESWL and surgical treatment.

PRESENT STATUS OF ESWL AND FACTORS DETERMINING ITS OUTCOME

Extracorporeal shock wave lithotripsy was first used in the therapy of gallstones in 1985 in Germany.² Since then it has been shown to be an effective and safe, non-invasive method of gallstone treatment in selected patients. The fact that ESWL can be performed on an outpatient basis increases its attraction as a non-surgical alternative.³ It is still being fine-tuned with respect to the optimal number of both shock waves and treatment sessions. In addition, the question of the efficacy of adjuvant bile acid therapy is being investigated. Improved lithotriptors have enhanced the ability to fragment stones faster and with less discomfort to the patient. Analgesia, sedation and/or anaesthesia are often not needed, especially with the use of piezoelectric devices.³

The successful outcome of ESWL is, to a large extent, determined by the degree of fragmentation.^{4,5} Gall-bladder clearance of gallstones improves and stone recurrence decreases with decreasing fragment size. Patient selection is a most important modifier of ESWL, with radiolucency and number and size of stones being the critical determinants of the efficacy of the treatment. Gallstones that are radiolucent (i.e. predominantly composed of cholesterol, and not larger than 2 cm in diameter) give the best success rate. Emptying, as well as residual and fasting volumes of the gall-bladder are other factors that influence the outcome of ESWL.

RELATIONSHIP BETWEEN COMPLETE FRAGMENTATION OF GALLSTONES AND THEIR CLEARANCE FROM THE GALL-BLADDER

Originally, ESWL was thought to be an extension of oral litholytic therapy, with lithotripsy fragmenting stones into smaller particles, thus enlarging their surface for bile salt action. However, this concept needs to be modified in view of the markedly improved rates of gallstone clearance which have been reported recently with the use of a technique called pulverization. Advances in lithotripsy technology have made it possible to fragment stones into very small, sand-like particles (pulverization),^{4,5} which clear the gall-bladder faster than large fragments. Pulverization is accomplished by increasing the number of shock wave sessions and repeating the procedure until stones are finely disintegrated. The rationale of this strategy is based on the expectation that small, sand-like gallstone fragments can easily pass through the cystic duct, which measures approximately 3 mm in diameter.⁶ It is important to note that in the studies, in which pulverization was accomplished, analgesia or sedation was often not used, in spite of up to ten treatment sessions. Consistent with previous studies, stone size and number were the impor-

tant determinants of gallstone clearance, although the stones treated were larger in size and higher in numbers than in previous studies.^{7,8} Although excluded from previous lithotripsy trials, calcified stones were treated in a recent pulverization study with no adjuvant therapy.⁵ While the calcified stones took longer to pulverize, their clearance was roughly equal to that of the non-calcified stones. The disappearance rate of solitary 1–20 mm uncalcified gallstones was 87% in 4–8 months and 100% in 12–18 months. The corresponding clearance of solitary 1–20 mm calcified gallstones was 72 and 80%, respectively. However, at 18–24 months, the disappearance rate of calcified stones had increased to 86%. This study correlated with a previous report that showed rapid clearance of a fragmented calcified stone.⁹ This observation differs from previous reports, which indicated that calcification leads to a decreased stone clearance.^{10,11}

In two of the three studies^{4,5,12} in which pulverization was used, more than 90% of the patients were ultimately stone free. In the third study, 86% of the patients with <2 mm fragments showed complete stone clearance within 6 months.¹² With an impressive gallstone clearance in selected patients, most recent ESWL studies are very encouraging, particularly as they included a substantial number of patients who would have been excluded in previous studies (i.e. those with calcified, larger (>2 cm), and multiple (>3) stones.

Role of adjuvant oral bile acid therapy in ESWL

Extracorporeal shock wave lithotripsy of gall-bladder stones was introduced in conjunction with the adjuvant use of oral litholytic agents. As ESWL was considered mainly a procedure that improved the dissolvability of gallstones by bile acids, and as bile acid therapy is effective only in non-calcified cholesterol stones, ESWL treatment was confined to this type of gallstone. Therefore, the majority of ESWL involved bile acid therapy, the use of which was considered essential. However, two recent studies provided evidence that adjuvant bile acids may not be necessary in most cases in which pulverization of the gallstones is achieved. In these studies, complete disappearance of gallstones was observed in up to 100% of the patients with pulverized stones who did not receive adjuvant bile acid treatment.^{7,9,10} A Danish study,¹³ along with Tsuchiya *et al.*,¹² showed no significant improvement in stone clearance in patients undergoing ESWL with the use of adjuvant bile acid therapy. This may be related to the finding that ursodeoxycholic acid increases both fasting and residual gall-bladder volume with a reduction in the ejection fraction.¹⁴ These changes in gall-bladder contractility could promote stone retention and growth. In a cost-benefit analysis of adjuvant bile acid therapy, Nicholl *et al.* noted a slight increase in gallstone clearance, but no improvement in symptom relief.¹⁵ In addition, a study in Quebec concluded that bile salt therapy was not indicated for routine use after ESWL.¹⁶

However, this study had an unusually high drop-out rate, the reason for which related to both the cost and length of bile acid treatment of gallstones. The role of bile acid treatment as an adjuvant to ESWL needs to be further evaluated in studies in which pulverization of the gallstones is accomplished.

In addition to its role as an adjuvant post ESWL, bile acid therapy has also been studied in respect to its effects on gallstone fragmentation and clearance if administered prior to lithotripsy.^{17,18} Wehrmann *et al.* reported no significant difference in stone shape or cholesterol content with regards to fragmentation efficacy when pretreating gallstones *in vitro* with bile salts compared with controls. Furthermore, the difference in the number of shock waves required for fragmentation to <2 mm was not appreciable between the two groups.

GALL-BLADDER FUNCTION

Normal gall-bladder contractility, a patent cystic duct and an intact gall-bladder wall, are prerequisites for the performance of ESWL. The procedure itself does not seem to have anything more than a brief, transient effect on gall-bladder function.^{19,20} Gallstone patients have been shown to be characterized by a higher fasting and residual gall-bladder volume.²¹ It can be theorized that these changes may result in bile retention with a consequent risk of stone formation. In contrast, good gall-bladder emptying appears to promote gallstone clearance after ESWL, as shown by the finding in one study that patients with good gall-bladder contractility cleared the gallstones in one-third the time of those with impaired gall-bladder function.²²

Fasting and post-prandial serum levels of cholecystokinin have been found to be normal in patients with gallstones.^{21,23} Impaired gall-bladder motility in gallstone patients did not improve after intravenous infusion of cholecystokinin or ingestion of a meal, suggesting a defect in end-organ response.²⁴ The gall-bladder dysmotility in gallstone patients is thought to be due to a disturbance in transmembrane signal transduction. *In vitro*, the reduced contractility can be overcome with injection of the second messenger inositol triphosphate into gall-bladder smooth muscle.²⁵ Prokinetic agents, such as erythromycin and cisapride, have been used experimentally in animals and humans to increase gall-bladder emptying. However, a recent study in humans, which showed no improvement in gall-bladder emptying,²⁶ conflicts with an earlier report which had indicated a prokinetic action of this compound on the gall-bladder.²⁷ More studies are needed to determine whether prokinetic agents are effective in promoting gall-bladder emptying.

GALLSTONE RECURRENCE

Gallstone recurrence rates post lithotripsy have been described to vary from 11 to 26% for a 24-month period using actuarial analysis.^{28–30} In most studies,

stones continue to recur as patients are followed after ESWL. However, the rate of recurrence usually declines with increasing length of follow up and rarely exceeds a total of 50 to 60% cumulatively.^{28–30} In patients with single stones, the recurrence seems to be lower than 50%. Furthermore, stone recurrence may be significantly reduced by application of the described pulverization method. In the vast majority of ESWL studies, oral litholytic therapy with bile acids was used for 3 months after complete stone clearance. Previous studies were not able to prove consistently that factors, such as age, sex, body mass or number of original stones, influenced gallstone recurrence. However, the same studies suggest that gall-bladder emptying, bile acid kinetics and genetics may be independent contributing factors in gallstone recurrence.

Gall-bladder emptying has been demonstrated in recent studies to be decreased or impaired in those patients that have recurrent gallstones. Gall-bladder ejection fraction, ejection rate and residual volume, in contrast to fasting volume, showed consistent differences between the subjects who did and those who did not have recurrent gallstones.^{31–33} Impaired emptying of the gall-bladder, which provides more time for the nucleation and crystallization of cholesterol and/or bilirubinate to occur, facilitates the formation of gallstones. Nevertheless, not all patients with normal gall-bladder contractility remain free of gallstones, indicating that factors other than gall-bladder motility are involved in the formation of gallstones.

Enhanced conversion of cholic acid (CA) to deoxycholic acid (DCA) was seen to be an indicator for reformation of gallstones in one study.³¹ Cholic acid was demonstrated to degrade more rapidly to DCA in subjects with recurrent stones, than in stone-free controls. This irregularity in bile acid kinetics, which leads to a reduced size of the CA pool and to an expansion of the DCA pool, was seen in eight of 10 patients with recurrent stones, but in only three of 10 in the control group. Biliary cholesterol saturation increased with the level of DCA in bile. However, in the same report, the groups both with and without recurrence had supersaturated bile. Further studies are needed to define the role of disturbances of bile acid metabolism in the recurrence of gallstones.

Interestingly, there appears to be a genetic predisposition for the recurrence of cholesterol gallstones. Apolipoprotein E4 (apoE4) plays an essential role in the metabolism of cholesterol. The phenotypes of apoE4 are genetically determined by three alleles (E2, E3, E4) at a single locus on chromosome 19 and are associated to plasma levels of lipoprotein cholesterol. Indeed it has been shown that gallstone cholesterol content is related to apoE4 polymorphism. In one study, a 2.4-fold increase in gallstone recurrence was found in patients with the apoE4 genotype.³³ A possible explanation for the findings may be that apoE4 is involved in the intestinal absorption of cholesterol and its redistribution in the body. Apolipoprotein E4 genotypes showed the highest intestinal absorption of cholesterol, but the lowest rate of hepatic synthesis of bile salts, a pattern which would favour the development of bile supersaturation in cholesterol.

Cost-effectiveness of ESWL versus cholecystectomy

As, in contrast to surgery, ESWL does not result in gallstone disappearance in all cases without a significant risk of stone recurrence, it cannot be equated with cholecystectomy. However, in its evaluation as an alternative to cholecystectomy in the treatment of gallstones in selected cases, ESWL needs to be compared to surgery with regard to both the health benefits and costs. In a randomized, prospective study by Nicholl *et al.*, lithotripsy was compared with CC.³⁴ In this study, 1-year health status, a subjective assessment measured by the Nottingham Health Profile, as well as symptomatic relief, were similar in the ESWL and CC groups, except that the improved health status was reached within 2 weeks in the ESWL group as opposed to 5 weeks in the CC group. In the CC patients, however, patients with small bulk stones < 4 cm had only half the health gains of the rest of the patients in the study. In contrast, only 22% of the patients randomized to lithotripsy in this trial were stone free, which suggests that fragmentation alone may improve symptoms. During the 12-month follow up, 5% of the CC group had major complications (bile leak, hemicolecotomy and subphrenic abscess), compared with 4% of ESWL patients (all acute cholecystitis) requiring hospitalization. Biliary colic was experienced significantly more often in the ESWL group (34%) than in the CC group (18%). It is important to note that in this study 39% of the lithotripsy patients had gallstones greater than 4 cm, and that 23% had calcified stones. In a retrospective study, Go *et al.* compared cost-effectiveness of LC, CC and ESWL.³⁵ Subjective health outcome differed significantly in this study. Persistent symptoms, such as biliary colic and abdominal pain, were reported by 59% of the ESWL group, but only by 11 and 14%, respectively, in the CC and LC groups. In contrast to the study of Nicholl *et al.*, which showed no relationship between achievement of stone freedom and the incidence of biliary colic,³⁴ symptomatic relief post-lithotripsy was significantly more common after complete disappearance of stones than in the presence of residual fragments. Bass *et al.* found the 5-year quality of life to be slightly better after ESWL than after CC for both patients with single stones and older patients with multiple stones.³⁶ They also found that, with increasing initial patient age, expected average survival was increasingly better for ESWL than for surgery.

Extracorporeal shock wave lithotripsy was seen, to different degrees, to be more expensive than surgery in all of the studies cited. However, in the study by Nicholl *et al.*, one-way sensitive analysis showed that ESWL was less expensive than CC if no bile salts were used and if the patient did not have to be admitted to the hospital.³⁴ As ESWL is an outpatient procedure and as bile salts may not be necessary in all patients, ESWL should be cost-effective, particularly in elderly patients with radiolucent, solitary and less than 30 mm gallstones. Elderly patients with multiple stones may also benefit from ESWL cost-effectively because relief of symptoms, rather than complete stone freedom, would be the main therapeutic goal in this population.

FUTURE OF ESWL FOR GALLSTONE TREATMENT

Although difficult to predict, the future of gallstone ESWL as a significant treatment modality depends, to a large extent, upon the interest of lithotripter manufacturers to sponsor further studies of the optimal application of this exciting technology in gallstone patients. The lack of such sponsorship has hampered the ability of investigators in the USA to provide the data necessary for Food and Drug Administration approval of ESWL for gallstone therapy. However, ESWL is used at a relatively constant rate in several medical centres in Europe, in particular, in Germany. Although we have only limited information regarding gallstone ESWL in Asia, it appears to be used in several countries, such as China and Japan.

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