SPECIAL ARTICLE

Extracorporeal Shockwave Lithotripsy of Gallbladder Calculi

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The last decade has witnessed the introduction of several new nonsurgical modes of therapy for gallstone disease. These include orally administered bile acids, contact dissolution with methyl tert-butyl ether (MTBE), and biliary extracorporeal shockwave lithotripsy (ESWL). These new non-surgical treatment modalities for gallstone disease, either individually or in combination, have significantly increased the number of patients in whom surgery can be avoided.

Dissolution of gallbladder stones with oral bile acids is limited by stone size and composition and the length of time required for complete stone dissolution. Contact dissolution of stones by MTBE has the major disadvantage of being an invasive procedure. ESWL is a relatively non-invasive treatment modality and several reports of its application in the treatment of gallstone disease are now available. The presently available data and our own clinical experience allow us to make important observations about its promise for the future and its possible limitations.

Patient Selection

Only radiolucent stones with collective measurement of 30 mm present in a functioning gallbladder with a patent cystic duct, as determined by oral cholecystography (OGC), are treated by most investigators (Table 1). This has followed from the original biliary lithotripsy protocol from the Munich Group calling for adjuvant oral cholestocholicysis with bile acids. The patency of the cystic duct is considered essential to ensure fragment passage and inflow of bile acids.

In this study the selection criteria were enlarged to include calcified as well as multiple (up to six) stones of all sizes (Table 1). Also ultrasound was used to assess the gallbladder function and cystic duct patency instead of OCG as a recently concluded study at our institution has shown that demonstration of 20% contraction of the gallbladder following a standard fatty meal is a good indicator of cystic duct patency.

Table 1: Biliary Lithotripsy Protocols

<table>
<thead>
<tr>
<th>Munich</th>
<th>FDA (USA)</th>
<th>Vancouver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptomatic patients</td>
<td>Symptomatic patients</td>
<td>Symptomatic patients</td>
</tr>
<tr>
<td>2. 1-3 radiolucent stones; Total</td>
<td>1-3 radiolucent stones; Largest stone</td>
<td>1-6 radiolucent or radiopaque stones; No</td>
</tr>
<tr>
<td>measurement &lt; 30 mm</td>
<td>&lt; 30 mm</td>
<td>limit on the number</td>
</tr>
</tbody>
</table>
| 3. Gallbladder                              | Gallbladder visualization on oral       | 20% gallbladder contraction on ultrasound,
| visualization on oral cholecystography      | cholecystography                        |                                         |
| 4. Normal coagulation profile               | Normal coagulation profile              | Normal coagulation profile               |
| 5. No acute complications of                | No acute complications of gallstone     | No acute complications of gallstone      |
| gallstone disease                            | disease                                 | disease                                 |
| 6. Adjuvant oral bile acids                 | Adjuvant oral bile acids                | No bile acids                            |

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Table 2: Results of ESWL of Gallbladder Calculi from Some Selected Centers

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>No of patients</th>
<th>Oral bile acids</th>
<th>Percent stone free at follow-up (no.)</th>
<th>Stone demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sackman</td>
<td>175</td>
<td>yes</td>
<td>80</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>604*</td>
<td></td>
<td></td>
<td>single or up to three radiolucent stones with total measurement ≤ 30 mm.</td>
</tr>
<tr>
<td>Greiner</td>
<td>157</td>
<td>yes</td>
<td>42</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>707*</td>
<td></td>
<td></td>
<td>single &lt;20 mm radiolucent stone</td>
</tr>
<tr>
<td>Ponchot</td>
<td>135</td>
<td>yes</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Ehl</td>
<td>75</td>
<td>yes</td>
<td>53</td>
<td>NA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>single or up to three stones with measurement ≤ 30 mm</td>
</tr>
<tr>
<td>Bory</td>
<td>101</td>
<td>yes</td>
<td>35</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>single or multiple radiolucent stones with total measurement ≤ 50 mm</td>
</tr>
<tr>
<td>Burhenne</td>
<td>136</td>
<td>no</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>280*</td>
<td></td>
<td></td>
<td>1 to 6 radiolucent or radiopaque stones, 5 mm to no upper limit in size</td>
</tr>
<tr>
<td>Multicenter Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barnett</td>
<td>223</td>
<td>yes</td>
<td>40</td>
<td>NA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-40 mm size radiolucent stone</td>
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<tr>
<td>Delmon</td>
<td>212</td>
<td>yes</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21-40 mm size radiolucent stone no limit on stone number</td>
</tr>
<tr>
<td>Albert</td>
<td>60</td>
<td>yes</td>
<td>50</td>
<td>NA</td>
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<td></td>
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<td></td>
<td></td>
<td>single or up to three radiolucent or radiopaque stones</td>
</tr>
<tr>
<td>Baron</td>
<td>223*</td>
<td>yes</td>
<td>34</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>single or multiple radiolucent stones with total measurement ≤ 30 mm</td>
</tr>
</tbody>
</table>

* Results updated or obtained at the Third International Symposium on Biliary Lithotripsy, Munich, September 13-15, 1990
† Data available from only 2 of the 4 centers
NA Results not available.

Clinical Results

Results from several large studies,3,15,22 (Table 2) show gallbladder clearance rates of 29 to 80% at six months. Our success rates of 45% and 60% at six and twelve months, respectively, without adjuvant oral bile acids compare favorably with those of others who rely on chemolitholysis for fragment clearance. This similarity in treatment outcomes is probably explained by the high number of shocks (up to 20,000) received by our patients to ensure that all fragments measured less than 3 mm. The minimum fragment size is more critical in our patients since no further dissolution is expected and the spontaneous passage is presumably the only mechanism of clearance. The average number of lithotripsy sessions per patient, thus, was 2.7 in our patients23 as compared with nearly 1.0 in most other centers which restrict the number of maximum shock waves and treatment sessions.3,12,15 Achievement of minimum fragment size is not mandatory in their patients as further dissolution is expected with bile acids.

Role of adjuvant bile acids

As the experience with ESWL grows, the role of expensive adjuvant bile acids needs to be clearly defined. At present, no controlled data are available regarding their contribution to the disappearance of gallstones after lithotripsy. The efficacy of bile acids was already established in the treatment of certain cholesterol gallbladder stones, lithotripsy was initially used in those patients as an adjuvant to bile acids. Shockwaves fragment gallstones and expose a larger surface area of the stone for dissolution by bile rendered unsaturated with bile acids. The disappearance of fragments from the gallbladder is also aided by fragment passage through the cystic and common bile ducts into the duodenum. We have noticed that some patients pass residual fragments quickly, while in others, these tend to be retained in the gallbladder. Occasionally, fragments may even increase in size. It is reasonable to believe that the former category of patients can be treated without any oral bile acids, whereas bile acids may be started in the latter groups at appropriate time during follow-up. The added mechanism
of dissolution would aid fragment clearance in these patients. This practice would be more economical and avoid use of bile acids in those patients in whom fragments pass satisfactorily.

Stone Burden

Various controlled clinical trials have also shown that the rate of satisfactory fragmentation is related to the original stone size and number. Two in vitro studies have demonstrated that the total stone burden is the major predictor of successful fragmentation of human gallstones, the percentage of stones that were successfully fragmented decreasing with increasing stone diameter, from 100% for 6-10 mm stones to 15% for stones 26-30 mm in diameter. Success rate or complete fragment clearance rate also depends upon the size and the number of stones. The Munich Group has shown a success rate of about 70% in patients with solitary stones less than 20 mm in diameter, 40% in patients with solitary stones 21 to 30 mm in diameter, but only about 20% in patients with two or three stones at four to eight months after lithotripsy. The corresponding figure at 12 to 18 months post-lithotripsy were 85%, 75% and 60%. Our success rate in patients with solitary 5 to 40 mm size stones is about 60% and for two or more stones, about 30% at 12 months follow-up. Patients with multiple calculi require a longer follow-up for fragment clearance.

Fragmentation of numerous large calculi produces a large amount of sludge which attenuates the shockwave energy, thus inhibiting adequate disintegration of large fragments. Perhaps a more important factor is the inability to visualize and target by ultrasound large fragments lying underneath the dependent sludge. In our clinical practice with large or multiple calculi, we allow a time interval of four to six weeks between lithotripsy sessions in order to permit passage of sludge and tiny fragments thus allowing better visualization and adequate fragmentation of the remaining large fragments during the subsequent lithotripsy treatment session.

Calcified stones

Because only cholesterol stone fragments are susceptible to adjacent dissolution therapy, patients with radio-opaque calcified stones have been excluded, with a few exceptions. Our preliminary experience with first 38 patients shows that lithotripsy appears to be as effective in the treatment of certain categories of calcified gallbladder calculi as in noncalcified stones. The calcified stones which respond quite favorably to shockwave therapy are dense and homogenously calcified. Stones with dense laminations are relatively resistant to shock waves.

Fragment dissolution with MTBE

Research efforts by several investigators directed towards more rapid dissolution of noncalcified gallstones have led to the technique of instillation of an ether solvent, methyl tert-butyl ether (MTBE), by a catheter placed directly into the gallbladder by the transhepatic route. A relatively high proportion of the gallstone population is suitable for this treatment as the number and size of stones do not seem to be limiting factors. Moreover, the necessity of demonstrating adequate function and contraction of the gallbladder is also bypassed. Transhepatic placement of the catheter makes it a less invasive procedure with a risk of bile leakage into the peritoneal cavity. The high lipid solubilizing property of MTBE endangers tissue necrosis or hemolysis if it is accidentally infused into the liver parenchyma or a blood vessel. Nausea, vomiting and duodenitis have also been reported consequent to the passage of MTBE into the intestine. Thus the exact role of adjunct MTBE therapy is presently uncertain.

Clumping of fragments

It is not infrequent, following successful fragmentation of gallbladder calculi, to observe clustering and clumping of fragments on ultrasound examination, which gives the impression of a large intact stone or a fragment. This often leads to unnecessary repeat lithotripsy sessions, unduly increasing the cost of treatment. Assessment of fragmentation can more accurately be made one hour after lithotripsy when fragments and sludge settle down in the dependent portion of the gallbladder. This one hour time period is probably too short to allow clumping of the fragments. This step could save another hospital visit for follow-up ultrasound. It seems probable that these fragments are joined over the next few days by the mucin in the bile which has been shown to be a constituent of certain gallstones. It has been postulated that mucin acts as a glue in the gallstone structure, and that it accelerates the nucleation of cholesterol in the bile.

Gallbladder contractility and role of cholecystagogues

Changes in the contractile function of the gallbladder may play a role in the formation of gallstones. Incomplete emptying may promote retention and, consequently, growth of cholesterol and bilirubin crystals in the gallbladder. To date, little is known about the change in the contractility of the gallbladder, if any, following lithotripsy. Speigel et al observed no change at day one and one year post-lithotripsy, however, a limited number of shockwaves (1500) were administered to each patient. In a recently concluded study, we investigated change in the gallbladder contractility, one month after administration of an average of 10,300 shockwaves, in 30 patients with gallbladder...
calciu. The gallbladder contractility decreased in 11 (22%) patients.\textsuperscript{35} In addition, there was an average 28% reduction in the fasting gallbladder volume following lithotripsy. Twenty-six (13%) patients had complete obliteration of the gallbladder lumen due to gallbladder contraction after lithotripsy, as seen at 48 hour follow-up ultrasound.\textsuperscript{35} The gallbladder remained contracted for 2 to 15 months in these patients. This contraction of the gallbladder is usually preceded by an attack of biliary colic.

It seems logical that stimulation of gallbladder contraction might accelerate fragment clearance in these patients through simultaneous increasing of the risk of cystic or common bile duct obstruction due to passage of large fragments from the gallbladder. Development of methods for inducing gallbladder contraction, without increasing the risk of causing obstruction at the narrow portions of the extrahepatic bile ducts, may be an important development towards more efficacious cholelithotripsy.

**Pain**

During lithotripsy, the patients usually experience pain at the front, which is superficial in nature; deep inside the gallbladder region; or in the back in the spinal or paraspinal region. Although pain can be alleviated with the help of intravenous analgesia and sedation, minor adjustments in the treatment position or in the angle of the shockwave head can also decrease its intensity or totally eliminate it.

Superficial cutaneous pain can be minimized by the liberal use of ultrasound gel which provides adequate coupling of the therapy unit with the skin. Since this gel tends to disperse with administration of shockwaves, frequent application is required. Pain referred towards the chest wall or pelvis can sometimes be effectively controlled by transthoracic electrical nerve stimulation electrodes which are placed on the chest wall or on the back in the midline at spinal level. Neural stimulation probably acts by promoting the release of endogenous neural hormonal substances such as endorphins.\textsuperscript{36,39} Deep pain inside the gallbladder region often requires increasing dose of intravenous analgesics and may or may not be associated with nausea. This type of pain is seldom relieved by repositioning and changing the angle of the therapy head. Pain in the back arising from the spinal nerve roots being struck by shockwaves can be helped by repositioning the patient in a more steep left posterior oblique position or in a left lateral position (depending on location of the gallbladder) and then changing the angle of the shockwave path such that the exiting shockwaves are directed away from the spine.

Mild post-lithotripsy local pain and discomfort, persisting for a day or two, is experienced by most patients and may occasionally require oral analgesics. Pain occurring beyond this period is most likely to be colicky in nature and is usually associated with fragment passage. The incidence of biliary colic following lithotripsy is reported to be 35% by the Munich group.\textsuperscript{3} Oral bile acids have been shown to decrease gallbladder motility and consequently diminish the episodes of biliary colic.\textsuperscript{37} Bile acids help in fragment clearance by dissolving them, hence this mechanism of fragment clearance is devoid of pain. On the other hand, fragment clearance due to their passage through the cystic and common bile ducts is usually associated with pain. In our center we do not use oral bile acids as adjuvants to dissolve residual fragments, and rely on fragments to pass through the narrow cystic and common ducts. Perhaps due to this reason, incidence of pain in our patients appears to be higher, although no controlled data are available, to date. Surprisingly, however, the rate of the complication which is associated with passage of fragments (acute pancreatitis) is about the same in our patient group (1.5%)\textsuperscript{31} as reported from other centers (1%).\textsuperscript{38}

**Complications and their management**

Animal experiments have proven the safety of biliary extracorporeal shockwaves.\textsuperscript{38,39} Minor complications in the form of hematuria in 2 to 5%,\textsuperscript{3,35,36} mild transient cutaneous petechiae in 11 to 39%,\textsuperscript{3,31,36} and transient elevation in the liver tests, lipase and amylase in 0.5 to 6%\textsuperscript{36} appear to be within acceptable limits. Incidence of biliary colic\textsuperscript{3,35,36} during fragment passage and dissolution over 12 to 18 months is also not high (11-35%) considering that all patients were symptomatic before entering the lithotripsy program.

Acute cholecystitis and pancreatitis are serious complications of lithotripsy which occur due to obstruction of cystic or distal common bile duct secondary to the fragment passage. Incidence of these complications following lithotripsy is 1-2% and 1-3%, respectively.\textsuperscript{35,36}

Cholecystectomy is the accepted standard treatment for acute cholecystitis. In the event of acute pancreatitis, therapeutic efforts must be directed towards rapid disimpaction of the obstructed ampulla by early ERCP and endoscopic sphincterotomy.\textsuperscript{40} The success of endoscopic sphincterotomy in these patients is reported to be 90%\textsuperscript{41} with procedure related mortality of less than 1%.\textsuperscript{42} Other major complications following lithotripsy in our patients with gallbladder stones (n=250) were subcapsular hematoma (n=1), gallbladder hematoma (n=1), and obstructive jaundice due to impaction of gallstone fragment in the common bile duct (n=1). The hematoma resolved in both patients and no intervention was required. The patient with obstructive jaundice required hospitalization for four days at which time the fragment dislodged spontaneously and the patient improved clinically. This patient was readmitted
to the hospital one month later with the same complaints and at this time his gallbladder was removed. According to available reports, the incidence of surgical intervention following lithotripsy varies from 1% to approximately 9% in our patient group. The reasons for cholecystectomy in our patients were failure of fragmentation or inability to perform lithotripsy due to technical reasons, chronic pain and discomfort following lithotripsy, or complication of lithotripsy related to fragment passage (mainly acute pancreatitis).

Reurrence of gallstones

The future role of ESWL will strongly depend on the rate of stone recurrence. The early data on recurrence of stones following lithotripsy published by the Munich group show a rate of 11% within one year and 15 ± 6% at 2 and 3 years in a group of 123 patients who were followed up to 34 months (mean 16.5 months). These data were calculated by actuarial life table analysis and appear to be quite promising when compared with percutaneous and endoscopic dissolution recurrence rates of 9% to 15% and 13% at one and two years, respectively. All patients developing recurrent stones formed multiple small calculi and it raises the doubt about accuracy of sonography in detecting small tiny residual fragments which provided the nidus for the recurrent stones. Close analysis of these data reveal that the recurrence rates are lower in patients with single stones (4 of 52) than in patients with multiple stones (2 of 54). Changes in the size and number of the residual fragments contribute to the development of the recurrence and indicates that all patients who do not undergo cholecystectomy should be followed up with ultrasound examination for an extended period. Thus, it is advisable to perform a one-year follow-up ultrasound examination in all patients undergoing lithotripsy.

References


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