Piezoelectric lithotripsy and soft tissue injury. Safety limits in the experimental and clinical setting

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Abstract

Controversy surrounds the capacity of extracorporeal shock wave lithotripsy to cause soft tissue injury. This study examines the influence of different dosages of shock waves on the gall bladder in both humans and an animal model. Sixty one guinea pigs were divided into groups and subjected to different numbers of shock waves (6000, 24 000, and 48 000) at different frequencies (2.5, 5.0, 10, 20 shock waves per second) and sacrificed at different intervals. Soft tissue damage after lithotripsy seemed to be related to the number of shock waves administered. In addition, repeated administration of low dose lithotripsy (at weekly intervals for six weeks) did not seem to produce a cumulative injury. Finally, in the animals sacrificed one month after receiving high dose lithotripsy, no soft tissue damage was evident, indicating satisfactory healing. Thirty patients were subjected to either high dose (36 000 shock waves) or low dose (6000 shock waves) lithotripsy 24 hours before elective cholecystectomy. Both macroscopic and microscopic evidence of soft tissue injury were detected in a significantly higher percentage of patients who received a high dose in a single treatment ($p < 0.05$). The group who received repeated low dose lithotripsy showed no evidence of cumulative injury. We conclude that low dose lithotripsy produces minimal soft tissue injury and is safe when repeated up to six times at weekly intervals.

The introduction of extracorporeal shock wave lithotripsy has revolutionised the treatment of kidney stones.¹ Not surprisingly, it was not long before attempts were made to treat patients suffering from gall stones in a similar way. Early results in a selected group of patients have shown that it is possible to shatter gall stones and ultimately produce complete gall bladder clearance when lithotripsy is combined with longterm bile acid treatment.²⁻⁵

There are a variety of lithotripters being manufactured, and these machines often have very different specifications.⁶ Because the energy sources of the shock waves and their focusing systems differ, the resulting shock waves have different characteristics with each lithotripter. At the present time, shock wave generation is based on three different energy sources: spark gap, electromagnetic, and piezoelectric.⁶

As the exact mechanism of stone fracturing by lithotripsy is not fully understood, some of these machines are probably more efficient than others and some probably cause more soft tissue damage than others. Recently, our surgical unit was presented with the opportunity to evaluate a

second generation piezoelectric lithotripter for use on gall stones.

Before extracorporeal shock wave lithotripsy could be considered as a realistic treatment option for patients suffering from gall stones several questions had to be addressed. Of immediate importance was the apparent paradox between the ability of this technique to shatter gall stones and supposedly be harmless to soft tissue. Consequently, it was decided to study this prospectively by first examining soft tissue changes after lithotripsy in an animal model and then in a series of patients who received lithotripsy before cholecystectomy.

Methods

We assessed the safety limits of EDAP (Exploration development des applications de la physique) lithotripsy in both animal and human studies. Lithotripsy in both studies was carried out using the EDAP LT-01. This is a piezoelectric lithotripter where the shock waves are focused onto a region of approximately 5×23 mm in diameter. The focal region pressure is adjustable, from zero at lower power settings to 900 bars at the 100% power settings.⁷ The peak pressure dropped to 50% of its original value at the frequency settings above 1.25 shock waves per second. This was shown by Coleman and coworkers during pressure measurements on the EDAP LT-01 installed in our unit (personal communication).

ANIMAL STUDIES

Guinea pigs were used as the animal model, as they have a well developed gall bladder (approximately 1.2 cm in diameter in fasting animals), which could be visualised under ultrasound in 90% of the cases. During lithotripsy all animals were anaesthetised and maintained with thiopentone. They were shaved, positioned prone, and a block of hard jelly (3M, Sonicar Ltd) was placed between the anterior abdominal wall and the fluid filled dome containing the main ultrasound mechanism of the EDAP lithotripter. The animals were subjected to different numbers of shock waves and were sacrificed at different intervals to determine the immediate or delayed effects of different numbers of shock waves.

Shock wave power and frequency in all these studies were used at clinically relevant settings.

Postmortem examination was carried out by an independent examiner (IR) without knowledge of the dose administered. The macroscopic findings were recorded and subsequently the gall bladder, liver, stomach, and any other injured organs were fixed in 10% formalin for histo-

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logical examination. Serial sections were made and stained with haematoxylin and eosin.

Traumatic changes to the gall bladder and the neighbouring organs were quantified according to the macroscopic and microscopic changes. Macroscopic changes included haematomas to the gall bladder and the neighbouring organs such as the stomach, duodenum, and liver. Histological changes included congestion of vessels in the lamina propria, intramural haemorrhage, eosinophilic infiltrate, and small vessel damage. Animals were designated as injured or non-injured based on the presence or absence of macroscopic and microscopic changes.

Group 1 Low dose Animals in group 1 were subjected to 6000 shock waves administered at four different frequencies – namely, 2.5 (n=6), 5 (n=6), 10 (n=6), and 20 shock waves per second (n=6). All animals were sacrificed 24 hours after lithotripsy.

Group 2 Moderate dose Animals in group 2 (n=8) received 24 000 shock waves administered at 20 shocks per second. All animals were sacrificed 24 hours after lithotripsy.

Group 3 High dose Animals in group 3 received 48 000 shock waves administered at 20 shocks per second. Twelve animals were sacrificed at 24 hours to assess the immediate traumatic effects. A further eight animals were sacrificed at two weeks (n=4) and four weeks (n=4) to assess, firstly, the delayed effects of trauma and, secondly, whether these changes were reversible.

Group 4 Cumulative dose Animals in group 4 (n=9) received 6000 shock waves at 20 shocks per second. This was repeated weekly for six weeks. The total number of shock waves received by this group was 36 000 and the animals were sacrificed one week after the last lithotripsy session to assess the cumulative effect of this number of shock waves.

Statistical analysis was performed using the χ^2 test.

HUMAN STUDIES

We assessed soft tissue changes after lithotripsy in patients who were treated before elective cholecystectomy. Patients were fasted from midnight the night before lithotripsy, and placed prone on the custom designed lithotripter table containing the fluid filled dome. By continuous ultrasound monitoring we attempted to ensure that the beam remained on target during treatment. Written informed consent was obtained from all patients entering the study, which had hospital ethical approval.

Group 1 Low dose Ten patients were studied in group 1. There were four men and six women. All patients received 6000 shock waves (at a frequency of 2.5 shock waves per second and 100% power) in a single session.

Group 2 High dose Twenty patients were studied in group 2. There were eight men and 12 women. All patients in this group received shock waves at a frequency of 10 shock waves per second at 100% power for 20 minutes and at a frequency of 20 shock waves per second at 50% power for a further 20 minutes (total treatment time 40 minutes). The total number of shock waves received by this group was 36 000. This

method of application was based on an initial manufacturer's recommendation (personal communication). This method also allowed the delivery of the shock wave dosage during a reasonable period of time which did not cause undue patient discomfort.

Patients in groups 1 and 2 underwent laparotomy and cholecystectomy within 24 hours (range 15–29 hours) of lithotripsy. Macroscopic findings were recorded at operation and all gall bladders were sent for subsequent histological examination. None of the patients entered into the study had clinical evidence of acute cholecystitis at the time of lithotripsy. In addition, none of the patients required anaesthesia, sedation, or analgesia during or after treatment.

Group 3 Cumulative We assessed soft tissue changes in five patients (four women, one man) who were considered failures of therapeutic lithotripsy (failure of stone fragmentation after six lithotripsy treatments or only slight stone clearance with dissolution therapy after six months, or both) and subsequently underwent cholecystectomy. This group of patients received repeated therapeutic lithotripsy over six months and were considered failures because of insufficient fragmentation or clearance of the gall stone mass. All patients received a total of 36 000 shock waves (6×6000 shock waves per session), administered in divided doses at three weekly intervals (range 1–4 weeks) over six months.

No patient suffered any ill effects before cholecystectomy directly attributable to lithotripsy. All patients made an uneventful post-operative recovery and in particular suffered no respiratory, biliary, or renal complications.

Results

ANIMAL STUDIES (TABLE 1)

Group 1 Low dose lithotripsy Two animals in this group had mild haemorrhage in the gall bladder (8%). Histological examination of the gall bladders in these two animals showed intramural haemorrhage and congestion of small vessels in the lamina propria. The two animals injured in this study received shock waves at frequencies of 2.5 and 10 shock waves per second respectively.

Group 2 Medium dose lithotripsy Three animals in this group had haemorrhage in the gall bladder wall (33%), while the remaining animals had no evidence of injury. Histological examination in the injured gall bladders showed intramural haemorrhage, congestion of small vessels, and eosinophilic infiltrate. None of the gall bladders examined showed any mucosal disruption.

TABLE 1 Percentage injury in guinea pigs receiving different numbers of shock waves

Group	Shock waves	Frequency*	Sacrificed	No	% Injury
1	6 000	2.5/5/10/20	24 hours	24	8
2	24 000	20.0	24 hours	8	25
3 a	48 000	20.0	24 hours	12	100
b	48 000	20.0	2 weeks	4	25
c	48 000	20.0	4 weeks	4	0
4	6×6 000 over 6 weeks	20.0	1 week after last treatment	9	12.5

*Shock waves per second.

TABLE II Macroscopic findings at cholecystectomy in patients receiving previous lithotripsy

Organ	Low dose (n=10)	High dose (n=20)	Cumulative dose (n=5)
Gall bladder haematoma	1	14	–
Scarring	–	–	0
Duodenal haematoma	0	6	–
Gastric haematoma	0	2	–
Falciform haematoma	0	1	–
No injury	9	6	5

TABLE III Microscopic findings in postcholecystectomy gall bladders

Histological change	Low dose (n=10)	High dose (n=20)	Cumulative dose (n=5)
Fresh intramural haemorrhage	2	14	–
Fibrinous exudation	0	11	–
Arteriolar oedema	0	9	–
Fibrinoid necrosis of small vessels	0	9	–
Eosinophilic infiltrate	0	9	–
Muscle necrosis	0	1	–
Haemosiderin deposition	–	–	0
Fibrosis	–	–	0
Normal	9	6	5

Group 3 High dose lithotripsy All the animals in this group (n=12) had haemorrhage in the gall bladder (100%). This was also associated with liver haematomas (70%), gastric haematomas (8%), adrenal haematomas (8%), and kidney haematomas (8%). Histological examination showed severe intramural haemorrhage, eosinophilic infiltrate, and small vessel damage. In contrast to those that were sacrificed two weeks later (n=4), only one animal (25%) had haemorrhage in the gall bladder wall. Furthermore, when animals were sacrificed and examined four weeks after receiving high dose lithotripsy, none showed evidence of active, fresh, or old injury, or healing in the form of fibrosis, or haemosiderin deposition. The number of animals injured among those that received high dose lithotripsy and were sacrificed within 24 hours was significantly higher in this group than in group 1 or group 2 ($p<0.001$). Subsequent to high dose lithotripsy all animals survived and did not suffer any ill effects before sacrifice.

Group 4 Cumulative lithotripsy Only one animal (12%) had mild pigmentation in the gall bladder wall which was associated with haemosiderin deposition on microscopy.

HUMAN STUDIES

Group 1 Low dose Patients in this group received a lower number of shock waves and suffered less severe tissue changes. Only two cases showed mild bruising of the gall bladder while no trauma to neighbouring organs was seen (Table II). Histological examination of the gall bladders showed mild intramural haemorrhage in the two cases that had macroscopic injury (Table III).

Group 2 High dose Of the 20 patients studied in this group, 14 had evidence of macroscopic injury to the gall bladder ranging from small petechial haemorrhages on the serosal surface of the gall bladder to transmural haemorrhage extending to the free edge of the lesser sac (Fig 1A). In no case, however, did the tissue change extend through to the mucosal layer of the gall bladder. Mucosal preservation was a constant feature in all cases (Fig 1B, arrow). This is in contrast to the findings in cases of acute gall stone cholecystitis, which suggests that the changes shown in this study resulted specifically from the use of lithotripsy. In addition to the changes noted in the gall bladders, further tissue damage to other organs was noted. Haematomas were seen in the duodenum (n=6), gastric antrum (n=2), and the falciform ligament (n=1). Six cases showed no evidence of macroscopic injury to the gall bladder or other soft tissues (Table II). The number of patients with soft tissue injury was significantly higher in this group ($p<0.05$). All of the patients who suffered macroscopic gall bladder injury showed appreciable histological changes (Table III). These included fresh intramural haemorrhage (n=14) and fibrinous exudation and arteriolar oedema (n=9). In addition, extensive eosinophilic infiltration and fibrinoid necrosis (Fig 2, arrow) of the arteriolar wall were seen in nine cases. Finally, pronounced muscle necrosis was apparent in one case. As with the macroscopic findings, complete mucosal preservation was noted on each specimen. No specific microscopic changes were noted in the six patients in whom there was no evidence of macroscopic injury.

Group 3 Cumulative All patients in this group who were failures of therapeutic lithotripsy had received a total of 36 000 shock waves in divided doses over six months. There was no macroscopic damage to the gall bladder or the neighbouring organs at the time of cholecystectomy (Table II). In addition, subsequent histological

Figure 1: (A) Outer aspect of gall bladder showing dark haemorrhagic areas. (B) Transverse section of the gall bladder showing thickening and haemorrhage. Haemorrhage is largely subserosal, but also transmural.

Figure 2: Small artery in the centre of the field with extreme narrowing due to intimal oedema and haemorrhage. Surrounding tissue also shows oedema and haemorrhage.

examination of the gall bladders in this group showed no evidence of fibrosis which would suggest longterm damage (Table III).

Effect of lithotripsy on gall stones

At the time of cholecystectomy all gall bladders were opened and the contents examined for evidence of gall stone fragmentation after lithotripsy. Although the patients in the high and the low dose groups had undergone only a single treatment session, the majority showed evidence of stone fragmentation. Of the 20 patients in the high dose group, 14 showed some degree of fragmentation ranging from small fragments to varying quantities of biliary sand. Similar results were obtained in the low dose and cumulative study groups in which 10 out of 15 patients had evidence of stone fragmentation.

Discussion

Early results of gall stone lithotripsy are encouraging and these have been achieved with either a spark gap or a piezoelectric system.²⁻⁵ There are, however, few available data on the safety limits for extracorporeal shock wave lithotripsy for gall stones. The EDAP LT-01 lithotripter uses a piezoelectric system in which the shock wave is generated from 320 ceramic crystals. The generated shock waves are then aimed onto the gall stone, using ultrasound imaging. This lithotripter has a small focal region where the shock waves strike the target, and although this requires accurate localisation, less pain is produced, thus obviating the necessity for analgesia, sedation, or anaesthesia. In addition, the potential for tissue damage to surrounding structures is reduced.⁴

In our study we have shown that piezoelectric lithotripsy using the EDAP LT-01 has the capacity to produce appreciable soft tissue injury and the extent of injury is directly related to the number of shock waves delivered. Although our data are limited, the expression of injury seemed

to be independent of the frequency in the range we used (2.5 to 20 shock waves per second). But, despite the pathological effects of a large number of shock waves in both the human and the animal studies, no untoward clinical effects were sustained. Furthermore, healing appeared to be complete in the guinea pigs treated with 48 000 shock waves after four weeks with no evidence of residual damage of a macroscopic or microscopic nature. We should, however, emphasise that the extrapolation of results from guinea pigs to large species, such as humans, must be interpreted with extreme caution, given the difference in abdominal wall thickness.

These findings concur with those in similar studies carried out in our unit in which the effects of renal piezoelectric lithotripsy were assessed.⁸ No late kidney scarring was found in comparison to that which has been shown with spark gap generated shock waves.⁹ While residual kidney damage might be important, and has been implicated as a possible cause of hypertension,¹⁰ it is hard to see how gall bladder or localised liver lithotripsy might have a similar deleterious systemic effect.

Low dose lithotripsy of 6000 shock waves seems to produce negligible tissue damage, and this dose seems safe when using the EDAP lithotripter at a single session. It is particularly gratifying to find that there was no cumulative injury after repeated treatment (up to six at weekly intervals) at this dose. This has important management implications for patients with gall stones as it allows more than one attempt to fragment a solitary stone or group of gall stones.

While appreciating that the injuries that we have described are created by a particular piezoelectric lithotripter, we believe it is most important to document these, particularly as there are so many different lithotripters available on the market, and yet there is a relative paucity of published data on their safety limits in gall stone lithotripsy. In a canine model, Brendel and Enders showed some soft tissue damage of the gall bladder consisting of serosal and subserosal haemorrhage after lithotripsy using a first generation spark gap lithotripter.¹¹ But, in addition, over 80% of the animals in this study had obvious pulmonary haemorrhage located at the diaphragmatic surface at necropsy. In several animals haemorrhage was also noted in the liver and the gall bladder, although these lesions were less than 3 mm in diameter. Brendel and Enders concluded that most of these tissue changes were clinically irrelevant and that the only changes that would be of real concern would be the lung damage. In addition, it was suggested that even this type of damage could be prevented by accurate localisation of the shock wave beam.

Piezoelectric lithotripsy because of its small focal region should not affect relatively distant organs such as the lungs and kidneys in humans provided accurate targeting is maintained by the operator during lithotripsy. We did, however, experience distal haematomas such as in the duodenum and falciform ligament, but these occurred early in our experience and may represent inaccurate gall bladder localisation. Drifting of the shock wave beam during treatment is possible, however, and should be con-

stantly monitored. The histological features that we have described seem to be specific lithotripsy induced injuries. The changes that were found in patients at cholecystectomy were distinct from those that are associated with either acute or chronic cholecystitis. The exact cause of these changes is not clear. Investigators have suggested that they might be related to a process of cavitation.¹² Each time a shock front is reflected at an interface in tissues a compressive pressure pulse changes into a tensile one. If the tensile forces are strong enough, they may give rise to the phenomenon of cavitation, where the liquid is pulled apart to create a bubble.^{13,14} The passage of acoustic energy such as that generated by lithotripsy could cause these bubbles to expand and collapse with extreme violence, thus potentially causing cellular or soft tissue damage.

Clearly, more work needs to be done to assess the effects of lithotripsy at an intracellular level. Nevertheless, the findings of this study suggest that, while low dose gall bladder lithotripsy seems to be safe, caution should be exercised before lithotripsy is applied at higher doses in the belief that it is an essentially harmless technique. In particular, high dose lithotripsy should be avoided in cases of choledocholithiasis where structures such as the common bile duct and pancreas may be endangered.

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