

Cost effectiveness of adjuvant bile salt treatment in extracorporeal shock wave lithotripsy for the treatment of gall bladder stones

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Abstract

The relative cost effectiveness of adjuvant urso and chenodeoxycholic acid treatment in extracorporeal shockwave lithotripsy (ESWL) has been assessed as part of a pragmatic randomised controlled trial of ESWL as a treatment of gall bladder stones. Of the first patients with gall stone volume <4 cm³ randomised to ESWL in the main trial, 24 were randomised to have ESWL alone and 26 to have adjuvant bile acid treatment, one of whom died before the end of the 12 month follow up period. At 12 months after treatment, differences in gall stone clearance between ESWL alone (3/24 (13%) clear, 5 (21%) referred for surgery) and ESWL and bile acids (6/25 (24%) clear, 2 (8%) referred for surgery) were not significant ($p=0.36$, log rank test). Patients in both groups had substantial and significant health gains (according to biliary pain frequency and severity, Nottingham Health Profile scores, visual analogue scale symptom scores, and complications) but there were no significant differences between the groups. Improvements in both groups usually occurred within a few weeks of treatment and were unrelated to gall stone clearance. Costs were greater in the bile salt group (95% confidence intervals for estimated cost difference: £90 to £630). If the purpose of treatment is symptom relief rather than gall stone clearance then adjuvant bile salt treatment seems to be unnecessary.

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It is well known that the two bile salts, urso and chenodeoxycholic acids can dissolve small gall bladder stones¹ and their combined action may be more effective than either alone.^{2,3} The efficacy of these acids is determined primarily by the composition and size of the gall stones, with a more favourable response in small uncalcified stones. With this in mind, it has been conventional since the initial use of extracorporeal shock wave lithotripsy (ESWL) for gall bladder stones to give adjuvant bile acids to speed the clearance of the small residual fragments that result from ESWL.⁴

Although most researchers have found improved gall stone clearance rates using urso or urso and chenodeoxycholic acids in conjunction with ESWL,⁵⁻⁷ good clearance has

also been found with ESWL alone.^{8,9} Furthermore, although it has been suggested that ursodeoxycholic acid may be effective in reducing the number of biliary pain episodes after ESWL by an improvement in gall stone clearance rates,¹⁰ the effect of adjuvant bile acid treatment on health generally and the range of symptoms commonly associated with gall stones has not been assessed. Similarly, the health benefits of ESWL over and above those that can be achieved by bile salts alone have not been formally assessed.

As part of the larger trial comparing the cost effectiveness of biliary lithotripsy and cholecystectomy,¹¹ we were able to undertake a pragmatic randomised controlled study of the cost effectiveness of combined adjuvant oral bile acid treatment in lithotripsy on patient symptoms and general health status.

Methods

Over the two years from April 1988 to July 1990 all symptomatic patients with gall bladder stones referred to the nine consultant surgeons at the Royal Hallamshire Hospital, Sheffield, England and in the latter months to two local major hospitals, for whom elective cholecystectomy was indicated as the sole major operative procedure were assessed for entry to the trial. Exclusion criteria, which have been detailed elsewhere,¹¹ included a non-contracting gall bladder (less than 50% volume after a fatty meal) as well as other comorbidity, but there was not restriction on the number or size of stones or their calcification and many patients included in the study did not meet the 'Munich criteria'.⁴

Patients who consented to be included and who were eligible for randomisation in the main trial who had a gall stone bulk of 4000 mm³ or less were randomised to either cholecystectomy, lithotripsy alone or lithotripsy and bile salts. The last two groups form the bile salt subtrial patients.

TREATMENT REGIMENS

Patients were treated with up to a maximum of 3000 shocks at each session on a Wolf Piezolith 2200/2300 without sedation or anaesthesia. The following morning the state of the gall bladder, extent of stone fragmentation, and size of the common hepatic duct were assessed by ultrasound. The target fragment size was less than 3 mm diameter as assessed by the ultrasound, and the schedule was repeated on

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up to four consecutive days until adequate fragmentation occurred, which was achieved in all patients. Patients allocated to receive bile salts started them two weeks before lithotripsy at a dose of chenodeoxycholic acid 7.5 mg/kg, and ursodeoxycholic acid 6.5 mg/kg, both being taken in the evening. Six months after treatment patients not started on bile salts could be switched over if this was thought clinically advisable.

OUTCOMES AND FOLLOW UP

The outcome measures were McGill pain scores¹² and Nottingham Health Profile (NHP) scores,¹³ visual analogue scale (VAS) symptom scores, and complications, measured repeatedly at baseline, and at two weeks, five weeks, three months, six months, and 12 months after treatment, and gall stone clearance times. VAS biliary pain scores were also collected using pain diaries. To assess gall stone clearance, the patients were followed up clinically and by ultrasound weekly for the first month after ESWL and then at monthly intervals until one year after ESWL. Every patient whose stones had not cleared or who had not been referred to surgery at 12 months continued to be followed up in routine clinics and gall stone clearance times have been recorded whenever clearance has occurred. The gall bladder was taken to have cleared at the time of the first of two successive follow up examinations at which no radiological evidence of stone fragments was found.

The complications recorded were those that might have been associated with lithotripsy or bile salts (diarrhoea, abdominal pain, biliary colic, or acute cholecystitis) and which the patient reported had resulted in their seeking medical assistance, and thereby incurring costs.

As there was no reliable method of assessing compliance with the bile salt regimen, compliance was not assessed at follow up. In a pragmatic trial concerned with what might be expected to happen in practice this is not important with regard to the validity of the results but does put a limitation on their interpretation.

PATIENT NUMBERS

To have a 90% chance of detecting at a 5% significance value a difference of three months in mean gall stone clearance times, the bile salt subtrial protocol suggested that 80 patients should be randomly assigned to lithotripsy alone or lithotripsy with bile salts (40 in each group), and that an interim assessment should be carried out after the first 50 patients had been randomised.¹⁴ Emerging clinical practice elsewhere, however, had begun to suggest that bile salts were a necessary adjuvant treatment for stone clearance and, without reference to the trial results, random assignment in the bile salt subtrial was stopped at the interim assessment when 26 patients had been randomised to lithotripsy with bile salts and 24 to lithotripsy alone.

STATISTICAL ANALYSIS

The results have been analysed by intention to treat in accordance with the pragmatic nature of the trial, so that patients in the lithotripsy alone arm who were given bile salts after six months (as permitted in the treatment protocols) have been retained in the lithotripsy alone arm for the analysis. Similarly, patients from either arm who were referred for cholecystectomy have been retained in the analysis.

Patients referred for cholecystectomy preclude a simple comparison of gall stone clearance times. Instead, the proportions of patients in each subgroup referred for cholecystectomy, cleared, or not cleared by 12 months have been compared, and also gall stone clearance time curves have been computed using Kaplan-Meier 'survival' estimates and compared using the log rank test. For these clearance curves the patients referred for cholecystectomy have been treated as 'withdrawals'.

With regard to biliary pain, NHP scores, and gastrointestinal and other symptoms, each patient's response to treatment can be described by 'curves' showing the change in each outcome measured during the 12 month follow up period.

Both the mean and median of a summary measure of the health gain during the 'follow up period' (and 95% confidence intervals¹⁵) have been calculated, and the distributions of the summary response of patients in the two treatment groups have been compared using re-randomisation analysis of covariance tests of differences in the mean response adjusting for baseline values.¹⁶ (Mean responses at each assessment have also been calculated and these are available from the authors on request).

The mean summary responses of the two treatment groups have been compared rather than the median responses, even though the distributions are often distinctly skewed, because for many symptom scores the median response is zero in both groups even though one group has fewer respondents or fewer severe symptoms among responders than the other group.

Of the 300 assessments that should have been done (50 patients \times 6 assessments), only three were missed. In a few cases patients also failed to answer all the questions at an assessment.

COSTS

The marginal (or extra) costs of bile salts as an adjuvant treatment to lithotripsy were estimated as the difference in mean cost per patient between the bile salt arm and the no bile salt arm. The marginal cost is therefore the sum of the differences in all costs, and not only the difference in bile salt costs.

The total health care cost for each patient to the National Health Service in the United Kingdom includes the costs of a suitability assessment, lithotripsy sessions, ultrasound sessions, ward stay, bile salts, and any complications requiring health services. Little

TABLE I Baseline data

	Treatment group	
	Lithotripsy alone	Lithotripsy + bile salts
Number randomised	24	26
Died	0	1
Number of patients in analysis	24	25
<i>Personal characteristics</i>		
Age in years (median (IQR))	53 (41-63)	56 (46-65)
Sex (% female)	79	68
Marital status (% married)	96	92
Area of residence (% Sheffield)	92	76
Referral hospital (% Hallamshire)	100	88
Waiting time, days (median (IQR))	21 (18-28)	21 (19-27)
Main indication (% with biliary colic)	92	88
<i>Stone characteristics</i>		
% With calcified stones	21	28
Number of stones (%)		
1	42	50
2-3	29	12
4+	29	39
Stone bulk (mm ³) (median (IQR))	1065 (434-1931)	1146 (550-2352)
Radius of largest stone (mm) (median (IQR))	8.9 (6.4-15.4)	10.0 (6.7-14.1)

difference in the patient time costs between the two treatment groups was expected as they have the same treatment and follow up regimens, and these costs were not considered in the subtrial. Confidence intervals for the difference in mean costs have been calculated.

The general approach to costing services has been outlined elsewhere.¹¹

Results

EXCLUSIONS AND BASELINE COMPARISONS

Twenty four patients were randomised to lithotripsy and 26 to lithotripsy with bile salts. Only one patient, randomised to lithotripsy with bile salts, who died from lung cancer before the 12 months assessment was not followed up for the full year. Summary scores could not be calculated for this patient and the patient has been excluded from these analyses.

The two subtrial treatment groups had similar personal and stone characteristics (Table I).

GALL STONE CLEARANCE

By the end of 12 months, three (13%) patients in the no bile salts group were clear of gall stones and five (21%) had been referred for surgery (Fig 1A). Among the 26 patients who were randomised to bile salts in the subtrial one had died, six (24%) had cleared, and only two (8%) had been referred to surgery.

None of the patients whose gall bladders cleared had had calcified stones, and most of the patients who cleared (six of nine) had had a single stone initially. Among patients with a single uncalcified stone there was a striking contrast in clearance, five of eight (62.5%) patients in the bile salt group had cleared at 12 months compared with only one (12.5%) of eight such patients in the no bile salt group. Excluding the patients with calcified stones, the Kaplan-Meier estimate of clearance at 12 months in the patients not started on bile salts was 16% compared with 35% in the bile salt group (Fig 1B). Because of the small numbers, however, differences between treatment groups in outcome (surgery, stone free or not stone free) at 12 months could have occurred by chance ($p = 0.15$).

A further three patients in the no bile salts group and two patients in the bile salt group have become stone free since the end of the 12 month trial follow up period. All patients, however, in the no bile salt group who had not cleared or had not been referred for surgery were given bile salts six months after treatment in accordance with the protocol ($n = 6$) or after 12 months ($n = 10$).

COMPLICATIONS

In the bile salt group 14 (54%) patients reported complications or other adverse sequelae of intervention, compared with 11 (46%) of those receiving lithotripsy alone, a non-significant difference ($\chi^2 = 0.51$, $p > 0.5$). The groups each reported 26 contacts with medical services for these problems. The commonest sequelae were biliary colic and non-specific abdominal pain.

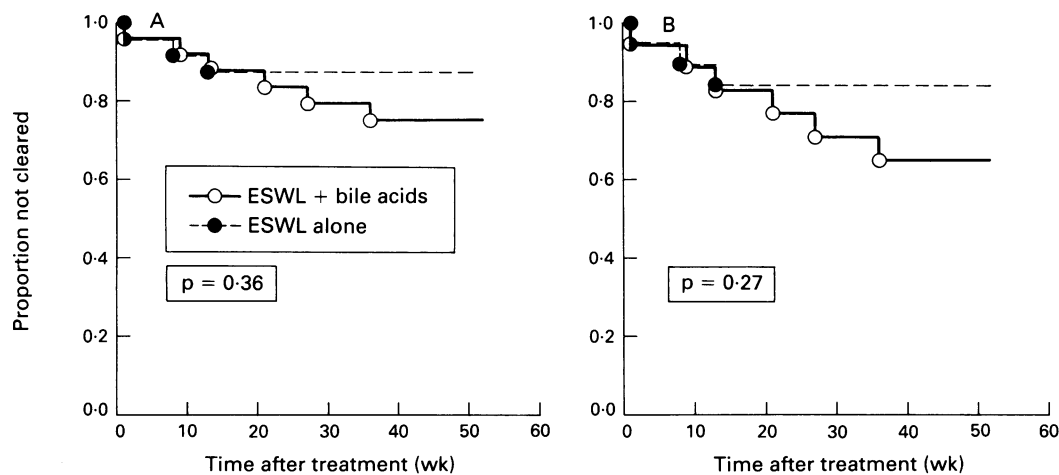


Figure 1: (A) Kaplan-Meier estimates of the proportion of patients whose gall stones had not cleared: * p value from log rank test for differences in clearance at 52 weeks; (B) Kaplan-Meier estimates of the proportion of patients with uncalcified stones whose gall stones had not cleared: * p value from log rank test for differences in clearance at 52 weeks.

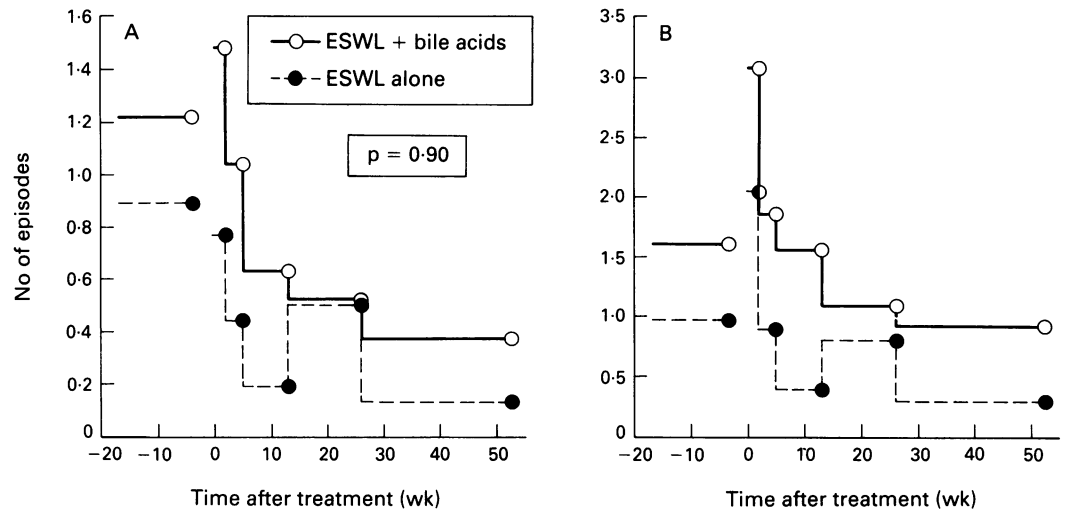


Figure 2: (A) Average number of biliary pain episodes per week per patient: *p value for the difference between treatment groups in numbers of pain episodes avoided; (B) average number of biliary pain episodes per week per patient reporting some pain since previous assessment.

SYMPTOMS AND HEALTH STATUS

After treatment both groups showed a significant reduction in the mean number of biliary pain episodes experienced, but there was no evidence of any difference between the treatment groups (Fig 2A). At baseline, 21% of those randomised to bile salts and 9% of those randomised to ESWL alone reported no biliary pain episodes in the previous three months. At the 12 month assessment, the proportions reporting no biliary pain in the previous six months were 63% and 57% respectively. Thus the reduction in the mean number of biliary pain episodes per patient was partly the result of fewer patients reporting any pain episodes, but it was also partly the result of there being fewer episodes per patient still experiencing pain (Fig 2B). Some patients who had previously reported pain ‘nearly every day’ claimed complete relief after treatment giving rise to large reductions in the mean number of

episodes pain per patient. The ‘average patient’ (represented by the median response), however, avoided fewer than the mean number of episodes. There was no evidence of any difference in medians between the two groups either. Similarly, the pain experience after treatment as recorded in the patients’ pain diaries was very similar in the two groups.

There were similar findings with regard to the symptom scores. Most symptoms showed a substantial improvement in mean VAS score between baseline and two weeks, and thereafter only small changes were seen (see Fig 3 for example) and the mean summary response for the 12 months after treatment showed significant health gains for most symptoms. For 10 of 14 symptoms assessed a better mean summary response was seen in the no bile salt group, however, after adjusting for baseline scores none of the differences between treatment groups were significant in either

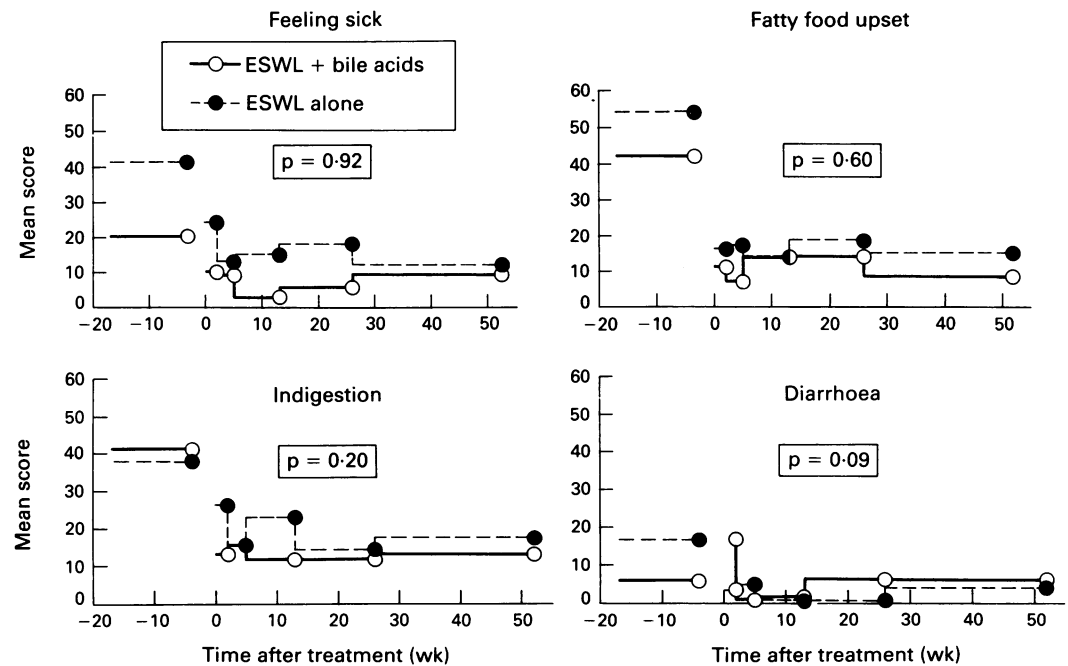


Figure 3: Mean VAS symptom score at six assessment times: *p values for the difference between treatment groups in the summary measure of health gain.

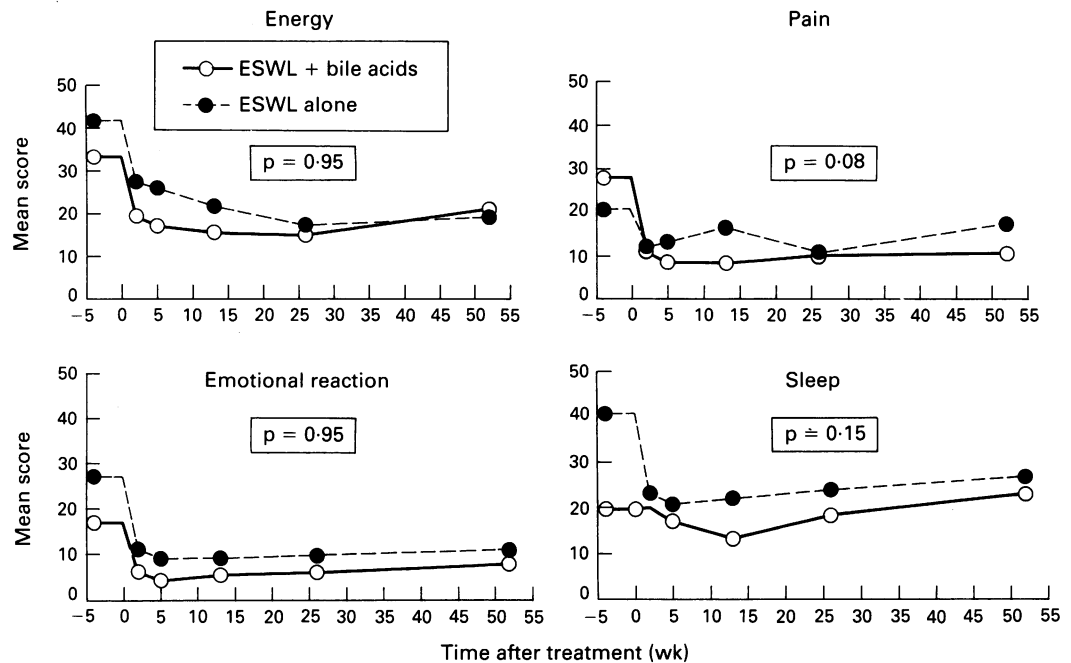


Figure 4: Mean NHP scores at six assessment times. **p* Values for the difference between treatment groups in the summary measure of health gain.

direction. A difference in the pattern of response for diarrhoea (Fig 3) was brought about by an increase in mean diarrhoea score in the bile salt group between baseline and two weeks after treatment, which had disappeared by five weeks probably as a result of reductions in the bile salt dose in patients having problems.

With regard to the Nottingham Health Profile scores, there were again reductions in nearly all dimensions in both groups between baseline and two weeks and thereafter little change, often resulting in significant health gains over the 12 months after treatment. The immediate health gain was especially noticeable for energy, pain, and emotional reactions (Fig 4) with only small reductions in the other dimensions. Of the six dimensions, five showed a better mean summary response in the lithotripsy alone group, the pain dimension being the exception. Adjusted for baseline response, however, none of the differences between treatment groups in either the pattern of response or summary response between the two groups were significantly different.

COSTS

The mean cost of the bile salt group exceeds that of the no bile salt group by £343 at six months, but only £256 at 12 months (Table II). This is mainly because of the cost of the larger number of cholecystectomies in the no bile salt group (five of 24 *v* two of 26), which has partly offset the difference in bile salt costs of £580. The 95% confidence intervals for the difference in mean cost at 12 months (-£90 to +£630) is wide, however, because of the small numbers in the trial; and the interval includes zero pointing to some uncertainty about the true difference in costs.

A sensitivity analysis found that the estimated marginal cost of bile salts as an adjuvant treatment to lithotripsy was insensitive to large variations in the unit cost estimates, including those for ward stay, medical fees, and the workload of the lithotripter. Unsurprisingly, the result is most sensitive to the price of bile salts, although even a price reduction of 25% would not reverse the direction of the result. A higher price for bile salts would, of course, have resulted in a larger and possibly significant difference in costs in favour of ESWL alone.

TABLE II Costs per patient at 12 months by treatment (1989/90 prices, £ sterling)

Service	ESWL + bile acids (n = 25)		ESWL alone (n = 24)	
	Quantity per patient	Cost (£)	Quantity per patient	Cost (£)
Suitability tests	1	83	1	83
Lithotripsy sessions	2.8	402	3.2	454
Ultrasound treatment sessions	2.8	15	3.2	17
Ultrasound follow up session	8.2	78	7.5	71
Ward stay	4.0	512	4.3	549
Bile salts	Prescription	681	Option to prescribe after 6 months	101
Re-treatment lithotripsy sessions	None	0	1/24	6
Cholecystectomy	2/26	111	5/24	302
Other complications	2/26	7	1/24	48
Mean total cost		1887		1631
Standard deviation		525		734
Range		866-3028		821-3667

Discussion

With respect to gall stone clearance, there was some weak though not significant evidence in favour of bile salts, as would have been expected a priori. Bile salts do dissolve stones and the combined treatment may act additively at least (if not synergistically) and in a larger trial it is probable that a statistically significant benefit in clearance times would have been found.

The expectation that after 12 months most patients would have cleared, thus permitting us to compare average clearance times, rather than merely the proportion who had cleared,

with just 40 patients in each treatment group, was unrealised. Plainly, the low clearance rates we have found were partly because of the heterogeneity of our patients. In the eight patients receiving bile salts with single uncalcified stones, five (62.5%) had cleared by 12 months. But in patients with multiple stones or calcified stones, little, if any, clearance occurred.

It is possible, also, that our patients only poorly complied with their bile salt treatment regimens and that this has diluted the apparent effect of bile salts. It is difficult to see, however, why compliance should have been worse in our study than in others, and, moreover, in routine clinical practice one could not expect compliance to be better than during the course of an intensively followed up trial.

As well as being related to adjuvant bile salt treatment and the stone burden, evidence from around the world suggests that, as would be expected, clearance is related to the fragment size achieved by ESWL, which may depend on both the lithotripter and the lithotripsy regimen used, and the shock wave energy used.¹⁷ We achieved adequate fragmentation¹⁸ in all trial patients, and in a concurrent study of a highly selected group of patients unsuitable for the trial, with single stones <20 mm in diameter, treated by ESWL with adjuvant bile salts, we achieved a 12 month clearance of 95% (unpublished data). It is unlikely therefore that the regimen explains the low clearance rates we found in the study. Furthermore, if the aim of treatment is symptom relief then clearance itself may not be important.

Overall, there is no evidence that patients meeting our broad eligibility criteria who had adjuvant bile acid treatment from the outset fared better in terms of symptoms than patients who were initially treated by ESWL alone, with adjuvant bile acids only introduced at six months if this was thought clinically necessary. There is no evidence of any benefit associated with bile acids with respect to any of the NHP health dimensions, nor with respect to any of 14 gastrointestinal and other symptoms often associated with gall stone disease, or with respect to biliary pain (reflecting the finding of an earlier study of the effect of ursodeoxycholic acid on pain experience after ESWL¹⁰). This is unlikely to be the result of the trial being too small. What differences were found were as often in favour of the no bile salts group as the bile salts group.

It is unlikely that the lack of any difference in improvement in self reported symptoms and health status between the treatment groups is the result of the small numbers of patients whose stones cleared in either treatment group. If this were the explanation then we would expect to see little improvement in either group. We have seen, however, substantial improvements in many self reported symptoms, including pain, and most dimensions of health, equally in both groups.

This effect cannot have been caused by the

bile salts as it is seen in both groups. It cannot be the result of stone clearance either, because it seems to occur almost immediately and thus before any stones are cleared. Between the baseline assessment (usually made at four weeks before treatment) and two weeks after treatment, nearly all the symptoms have resolved as much as they will ever go on to do despite the fact that at two weeks after treatment virtually all lithotripsy patients still have stone fragments in their gall bladders. Fatty food intolerance, for example, which was reported on average as about 40%-50% as severe as it could possibly be by the patients at baseline was reported on average as being only 10%-15% as severe as possible just two weeks after treatment. Twelve months later the VAS scores were the same as at two weeks before treatment. Furthermore, we have also found that the pattern of improvement in biliary pain episodes is the same in patients whose gall stones clear as in patients whose stones never clear.¹¹

It is possible that the improvement in health, which is rapid and similar in the two groups, and is thus neither the result of gall stone clearance or bile salts, is the result of the fragmentation of the stones, which did occur similarly in the two groups. Certainly if there were a critical stone number, size, shape, or even orientation that triggered symptomatic gall stone disease then it could be possible that stone fragmentation by lithotripsy would quickly relieve symptoms.

Another possibility is that the rapid improvement in health is the result of lithotripsy acting as a placebo. Presumably, a placebo effect is possible if the classic symptoms and health problems, which are reported to be associated with gall stone disease, and which we have measured here, are only weakly associated with the presence or absence of gall stones. There is evidence that this is the case both in the fact that most people with gall stones are symptomless,¹⁹ and that many people having had their gall bladders (and stones) removed continue to experience symptoms,²⁰ as well as the fact that the prevalence of upper right quadrant pain has been found to be unrelated to the presence of stones in the gall bladder.²¹ The fact, however, that the benefits of treatment that we saw were often sustained over 12 months may argue against a placebo effect.

The two main cost differences between the treatment groups were for bile acids and cholecystectomy. Bile acids may not be costly on a daily basis, but accumulated over a 12 month period they represented one third of the total costs in the bile salt trial arm. The higher number of cholecystectomies in the treatment group not started with bile salts could result from this group's lower gall stone clearance rate. The higher cost, however, of bile salts in the bile salt arm were only partially offset by the cost of these extra cholecystectomies in the no bile salt arm. The comparative costs of the two regimens were found to be insensitive to large variations in the unit cost estimates, and therefore the comparative costs are probably

relevant in most situations although the overall level of costs may be different.

Our results suggest that bile salts do not improve the effectiveness of lithotripsy in terms of symptom relief. It is possible, however, that they do improve stone clearance. Plainly, then, the extra costs of the bile salts can only be justified if the proportion of patients needing to be referred for surgery is reduced by adjuvant bile salt treatment. Our results do not suggest that this is the case, but the numbers are small and the confidence intervals for the cost differences wide. Nevertheless, if the aim of treatment is symptom relief then clearance would seem to be unimportant and bile salts unnecessary.

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