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THE COSTS AND EFFECTIVENESS OF EXTRACORPOREAL GALLBLADDER STONE SHOCK WAVE LITHOTRIPSY

versus

LAPAROSCOPIC CHOLECYSTECTOMY - A RANDOMIZED CLINICAL TRIAL

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March, 1995

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of M Sc.

ISBN 0-612-05529-9

Short title:

COST-EFFECTIVENESS OF LITHOTRIPSY AND LAPAROSCOPIC CHOLECYSTECTOMY

- Alan NG Barkun -

ABSTRACT

A randomized clinical trial was undertaken to compare the effectiveness and direct costs of shock wave lithotripsy (ESWL) and laparoscopic cholecystectomy (LC) for the treatment of symptomatic gallbladder stones. Over a period of 24 months, from a total of 468 patients screened, 35 patients [mean age:51.7±13.3 yrs, 71% female] were randomized to ESWL, and 25 [mean age:47.4±14.3 yrs, 80% female] to LC. 32 ESWL patients were treated, all as out-patients, with a mean convalescence post-ESWL of 0.5±1.2 days. In contrast, all LC patients were admitted to hospital for a mean duration of 2.8±1.5 days with a mean post-operative convalescence of 18.2±16.8 days as measured by research nurses. The patients in the ESWL group had an average of 1.3±0.6 stones (mean largest stone size 13.4±6.8 mm, total stone burden 16.4±6.6 mm). The mean number of lithotripsy sessions was 1.8±0.8 (range:1-3), and in 78% the fragmentation was satisfactory. These patients were also treated with a mean dose of 602±125 mg of ursodeoxycholic acid. Symptoms recurred in 22 (68%) patients in the ESWL group over a median follow-up period of 15 months. During this time, 6 of 32 ESWL patients (18%) experienced episodes of colic causing a day off work or away from usual daily activities. The two patient groups did not differ with respect to McGill Pain scores administered immediately after treatment. Three Quality of Life (QOL) tools improved similarly in both groups within the month following treatment. The only differences in QOL questionnaire results between both groups when administered 3 months following treatment and at six monthly intervals thereafter occurred for LC as greater incremental improvements were noted at 6 and 12 months follow-up ($P<0.01$). The overall stone disappearance

rate in the ESWL group after a median of 15 months was 38%. ESWL needed to be stopped prematurely in 3 cases. Two patients in the ESWL group developed pancreatitis during fragment dissolution, 1 needed endoscopic sphincterotomy for fragment removal. Ursodeoxycholic acid was terminated in 5 (16%) due to side effects. One (4%) LC patient developed recurrent colic in follow-up. The total disability duration was 6.8 ± 8.5 days for ESWL, and 22.7 ± 16.6 days for LC ($P < 0.01$). Despite this, 9 (28%) of patients have so far crossed over electively to the LC group. To date, only 45% of these have undergone LC with 3 years of follow-up. Direct costs to the Quebec Health Care system during the study period were determined by analysis of patients in both treatment groups. In 1993 canadian dollars, average costs and their range were 2,889$ (1,704$-5,830$) for patients undergoing LC, and 3,936$ (2,367$-6,243$) for patients treated by ESWL. The cost effectiveness ratios using the incremental differences in direct costs and duration of disability favoured ESWL at a cost of 58.9$/day of disability saved over the 15-18 months follow-up period. This ratio is particularly sensitive to variations in its denominator - the incremental duration of disability.

The effectiveness of ESWL is limited by its selective applicability, and modest success in achieving stone disappearance. However, disappearance of symptoms occurs despite persistence of stone fragments. Consequently, ESWL, results in a lesser duration of disability than LC over the first two years following treatment despite intermittent recurrences of biliary colic in a majority of patients. The therapeutic option of ESWL should be presented to all patients fulfilling its selection criteria. ESWL should especially be considered in patients refusing surgery, or those

in whom a prolonged post-operative convalescence following LC is anticipated. Further studies are required to better define the long-term clinical impact of stone persistence or recurrence.

ABRÉGÉ

Une étude randomisée clinique fut entreprise dans le but de comparer l'efficacité et les coûts directs de la lithotritie par ondes de choc (ESWL) et la cholécystectomie par laparoscopie (LC) dans le traitement des cholélithiases symptômatiques. Sur une période de vingt-quatre mois, parmi 468 malades évalués, trente-cinq malades (âge moyen: 51.7±13.3 ans, 25 [71%] femmes) furent randomisés au groupe d'ESWL, et 25 (âge moyen: 47.7±14.3 ans, 20 [80%] femmes) au groupe de LC. Trente-deux des patients du groupe d'ESWL furent traités, tous en externes, avec une convalescence moyenne post-ESWL de 0.5±1.2 jours. Les patients du groupe de LC restèrent à l'hôpital en moyenne pendant 2.8±1.5 jours et exhibèrent une convalescence post-opératoire moyenne de 18.2±16.8 jours telle que mesurée par les infirmières de recherche. Les patients du groupe d'ESWL avaient en moyenne 1.3±0.6 lithiases (taille moyenne de la pierre la plus grande 13.4±6.8 mm, charge lithiasique totale 16.4±6.6 mm). Le nombre moyen de séances de lithotritie fut 1.8±0.8 (1-3), et il y eut fragmentation satisfaisante dans 78% des cas. Ces patients furent traités avec une dose moyenne de 602±125 mg d'acide ursodésoxycholique. Les symptômes récidivèrent chez 22 (68%) patients du groupe d'ESWL lors d'un suivi médian de 15 mois. Durant cette période, six des 32 malades (18%) eurent des épisodes de colique nécessitant un arrêt de leurs activités journalières ou une journée de congé. Les deux groupes ne démontrèrent aucune différence dans les résultats du questionnaire de douleur de McGill administré immédiatement après le traitement. Trois évaluations de qualité de vie s'améliorèrent de façon similaire dans les deux groupes lors du mois qui suivit le traitement. Les seules différences dans les résultats

des questionnaires de qualité de vie entre les deux groupes administrés à trois mois de suivi, puis à intervalles de 6 mois par après, furent notés dans le groupe de LC où les patients démontrèrent des améliorations progressives plus importantes aux sixième et douzième mois de suivi ($P<0.01$). Le taux de disparition des lithiases dans le groupe d'ESWL fut de 38% après un suivi médian de 15 mois. La lithotritie fut arrêtée prématurément dans 3 cas. Deux patients dans le groupe d'ESWL eurent une pancréatite lors du traitement dissolvant, un de ceux-ci nécessita une sphinctérotomie endoscopique pour enlever un fragment cholédocien. La prise d'acide ursodésoxycholique fut arrêtée dans 5 malades (16%) à cause d'effets secondaires. Un patient (4%) du groupe de LC eut une récidive de colique biliare en suivi. La durée totale d'incapacité fut de 6.8 ± 8.5 jours pour l'ESWL, et de 22.7 ± 16.6 jours pour la LC ($P<0.01$). A ce jour, malgré ceci, 9 (28%) des malades randomisés au groupe d'ESWL ont décidé de subir une LC électivement. Cependant, seulement 45% de ceux-ci ont en fait eu une opération avec trois ans de suivi. Les coûts directs au système de santé du Québec durant la période de l'étude furent déterminés suivant une analyse des patients traités dans les deux groupes. En dollars canadiens de 1993, les coûts moyens et leur variation furent de 2,889$ (1,704$-5,830$) pour les patients subissant une LC, et de 3,936$ (2,367$-6,243$) pour les patients randomisés au groupe d'ESWL. Les rapports de coûts-efficacité utilisant les différences entre coûts directs et durées d'incapacité favorisèrent la lithotritie à un coût de 58.9$/jour d'incapacité épargné lors des 15-18 mois de suivi. Cette proportion est particulièrement sensible aux variations de son dénominateur: la différence en jours d'incapacité. L'efficacité de l'ESWL est limitée par la sélection restreinte des

malades, et les succès modestes de disparition de lithiases biliaires vésiculaires. Cependant, une disparition des symptômes se produit malgré la persistence de débris lithiasiques. La lithotritie résulte conséquemment en une durée d'incapacité inférieure à celle de la LC lors des deux années suivant le traitement malgré les récidives intermittentes de coliques biliaires chez la majorité des patients.

L'option thérapeutique qu'est la lithotritie des lithiases de la vésicule biliaire devrait être présentée à tout patient satisfaisant les critères de sélection. Le choix de la lithotritie doit tout particulièrement être considéré pour les patients qui refusent la chirurgie, ou pour ceux chez qui une durée de convalescence prolongée post-LC est anticipée. Une évaluation plus approfondie de l'impact clinique attribuable à la persistence ou la récidive de calculs doit faire l'objet d'études à plus long terme.

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STATEMENT OF ORIGINALITY

The review of literature described in this thesis includes work performed by the author in association with research groups at McGill University, and other institutions in the USA and France.

The main study described in this thesis represents original, as yet unpublished contribution to the field of gastroenterology and biliary surgery by the author who headed the McGill Gallstone Treatment Group. It is the only randomized clinical trial ever performed which compared ESWL to LC.

INTRODUCTION

Cholelithiasis affects 10-20% of the adult North American population (1). Although only approximately one fifth of all persons with gallbladder stones will need treatment (2,3), the expenditure to the American Health care System tops $5 billion dollars a year (4).

Over the past 7 years, a dramatic change has occurred in the approach to the treatment of patients with gallbladder stones which has included the development of extracorporeal gallbladder stone shock wave lithotripsy (ESWL) (5) and laparoscopic cholecystectomy (LC) (6,7). However, because of patient and peer pressures, this evolution has not always been driven by scientific rigor (8). Indeed, "turf" issues between different medical, surgical, and radiological specialties, hastily concluded economic analyses, and personal beliefs have dramatically influenced the development of these newer therapeutic technologies.

The McGill Gallstone Treatment Group was fortunate enough to study the treatment of gallstone disease during a temporal window of opportunity. This led to the completion of the first (and one of only two) randomized clinical trials comparing the mini-cholecystectomy to LC (9), and the only randomized controlled trial comparing ESWL to LC - the new gold standard treatment of cholelithiasis (10).

This thesis reviews the international data collected on the performance of ESWL, and attempts to define its cost, effectiveness, and consequent role in the management of gallstone disease using original results obtained from the completed randomized clinical trial mentioned above.

LITERATURE REVIEW

REVIEW AND CRITICAL APPRAISAL OF THE RELEVANT LITERATURE

Although the burden of serious morbidity and mortality due to gallstones is not great, the condition is intermittently painful and disabling, and it is estimated that in the United States alone, up to 15,000,000 persons may bear gallstones (1). Since the first cholecystectomy was performed by Carl Langenbuch in 1882 (11), many non-surgical treatments for the management of cholelithiasis had been developed, and there has been a recent resurgence in these with the advent of successful ESWL (12) and LC (6,7). In view of the benign course of most gallstones (2,3), and the safety and success of cholecystectomy (13), any new treatment modality must be rigorously assessed to evaluate its comparative efficacy, effectiveness, safety, and eventually cost-effectiveness. This has not been done so far with ESWL, perhaps because initially the success of lithotripsy of kidney stones had been assumed to extend to gallstones, and more recently because of the tremendous popularity achieved by LC (14,15). In fact, even LC itself has only recently been demonstrated to be superior to open cholecystectomy (9,16).

As a basis for the design, understanding of the justification and objectives of an evaluative clinical trial comparing ESWL to LC, and to aid in the interpretation of its results, we first review the epidemiology, natural history, and present surgical approach (the "gold standard") to the treatment of gallstone disease.

Gallstone disease

a. *Epidemiology*

Cholelithiasis is perhaps one of the so-called "Western diseases", and may reflect

a consequence of industrialization (17). The various quoted rates of cholelithiasis in the literature are difficult to interpret as autopsies, clinical studies, and prevalence surveys necessarily use different methodologies and examine different subpopulations of a given study group; hence they may be expected to yield different results. Despite this, most studies seem to confirm the following findings: The estimated worldwide prevalence of gallstones is misleading as it varies markedly from one population group to another. For example, the prevalence of gallstones is two-fold higher in females and the prevalence (probably in contrast to the incidence) increases with age (18). The reported prevalence of gallstones in most black African countries is less than 1% (19), whereas it is about 35% in Chile (20), and reaches 49% among the Pima Indians in Arizona (21). Such differences are attributed both to hereditary (Pima Indians) and environmental differences (Japan and Africa, for example), including the advent of a "westernized" diet (22,23). Even among European countries, prevalence rates vary widely, from 5% in Ireland to 38% in Sweden (18). Large differences have also been found within countries, such as India (24) and the United Kingdom (25). In North America, as elsewhere (for example, Japan, and Great Britain), reported prevalence rates, and probably the true underlying incidence rates, have increased significantly over the last 50-75 years. In New York, the prevalence of gallstones was 7.4% in 1903-12 and rose to 24.3% in 1959 (18). Similar increases have been noted in the U.S.A. as a whole (26) and in Scotland (27). The reported prevalence of gallstones in Canada doubled between 1961 and 1971 (18). This increase is explained in part by better diagnostic (ultrasound) and surgical techniques and perhaps increased use of medical services; changing demographic factors such as age and

sex may also be responsible for a part of the rise. A recent prevalence survey of a small town in Northern Italy, reported an overall prevalence rate of 11% (6.7% in men, and 14.6% in women) (28). The prevalence rates increased in this group from ages 18-29 to 50-65: for men from 1.1% to 11%, and for women from 2.9% to 27%. No recent prevalence surveys from Canada are available but we can extrapolate from the above data to estimate that approximately 1,500,000 women, and 750,000 men have gallstones in our country today. More recent mortality figures for Canada and their implication with regards to choosing outcome measures are discussed below.

The principal causative associations of gallstone disease include age, female sex (18), probably pregnancy (29), and obesity (29). Because of the increasing proportion of the aged in our society (30) and the increase in obesity (31,32), this number is expected to increase further with time. Yet only a fraction of these patients will require therapy, and to understand and select these, we must first review the natural history of gallstone disease.

b. *The Natural History of Gallstone Disease*

To best understand the outcome of untreated gallstone disease, and in order to select appropriate study groups of men and women with cholelithiasis, we must differentiate symptomatic from asymptomatic gallstones.

The silent gallstone: As the definition of gallstone-related symptoms in the literature has varied over the years, so have the recommendations for prophylaxis of the so-called "silent gallstone". Some authors have attributed non-specific symptoms such as

flatulence, belching, and fatty food intolerance to gallstones, but these are now thought to be equally frequent in the general population (28,33,34,35). Although the symptoms of biliary colic may be difficult to clearly delineate (36), a silent gallstone is now defined as one that has not caused biliary colic or complications directly attributable to its presence, such as pancreatitis, cholecystitis, or ascending cholangitis. About 80% of men and women with cholelithiasis remain asymptomatic (2,3,37). Life-table analysis demonstrated that about 10% of silent gallstones will cause symptoms within five years, 15% within 10 years, and only 18% within 20 years of the time of diagnosis (2). These results have been confirmed by other groups examining different patient populations (3,37-45), including patients with only mild symptoms (37). Although studies of the complications of silent gallstones have been analyzed only for small numbers of patients, the yearly risk of developing biliary colic seems to diminish with the passage of time (46). Moreover, the annual absolute incidence of gallbladder cancer in persons with gallstones is only about 9 per 10,000 person-years (47). Prophylactic removal of silent gallstones in the general population is therefore not widely recommended with the therapeutic alternatives presently at hand (2,3,38). What is not known, though, is whether some subgroup of patients exhibit a sufficiently higher risk of developing complications that early treatment would be advisable. This does not appear to be the case for diabetic patients (48,49).

The symptomatic gallstone: Symptoms seem to be first manifest at least two years after the onset of gallstone formation (50). The natural history of symptomatic stones has not been studied extensively, but appears to be less benign than for silent

stones (3). Up to one third of symptomatic patients will develop a complication with conservative management (51), and the surgical and post-operative morbidities are then increased (52). Women with cholelithiasis seem to develop symptoms more often than men (53). In the National Cooperative Gallstone Study's placebo group (untreated patients with symptomatic stones), 69% of the 112 patients experienced recurrence of symptoms over the next two years (54). Six percent of these patients had cholecystectomy during this time. It would appear that the rate at which symptoms recur decreases with the passage of time since 25 to 30% of patients are symptom free after 10 years, with a cholecystectomy rate of about 3% per year for the persons who remain symptomatic. On the basis of these data, treatment of patients with symptomatic gallstones is widely recommended.

Recent decision modelling has examined the impact of gallstone disease related mortality (55). The cumulative life-long probability of gallstone disease related death in a population of thirty year old males is 2%, most deaths occurring over age 65. The highly respected authors of this analysis concluded that "Some patients and physicians may decide that the risk of symptomatic gallstones is low enough that a policy of expectant management may be acceptable" (55). The "lesser" impact of gallstone related mortality when adopting a societal perspective is also demonstrated when examining canadian statistics as discussed below.

c. *The mortality attributable to cholelithiasis in Canada*

An assessment of mortality attributable to gallstone disease over a 35 year span

(1950-1985) was carried out, and limited to females, in whom the disease, at least early on, is more prevalent and in whom the case fatality ratio appears to be less than in males of similar ages. Based on considerations discussed above, it must be stressed that mortality represents only a limited aspect of the total burden of this disease in Canada. In contrast, in 1984-85, cholelithiasis was the second cause of separation for both sexes for all ages combined (Statistics Canada).

The age-specific deaths and corresponding age-specific crude death rates for cholelithiasis are shown in appendix. Although there were significant changes in disease classification up to the year 1975, these suggest that cholelithiasis kills mostly women aged 50 and more, and that the crude mortality rates have dropped markedly over the pat 35 years. In order to eliminate any possible influence of varying age distributions in Canadian females over age 50 from 1950 to 1985, the standardized mortality rates were calculated and confirmed these findings. The age adjusted mortality rates diminished steadily from 1950 to 1980 (1985 was the standard year). The increase in mortality rates noted from 1950 to 1955 is due to a significant change in the ICD classification of gallstone related deaths diagnostic categories. Following 1955 however, there was a gradual drop over the next 10-15 years. The large decrease noted from 1965 to 1970 was partly due to another ICD change in classification. Nonetheless, the overall trends is clearly downwards and confirms that the drop is not due to a change in the age distribution of the studied population over time. Cohort analysis demonstrated the lack of any significant cohort effect over time. Finally the analysis in potential years of life lost (PYLL) is also shown in appendix. A comparison of the direct age standardized

Table A: Age specific death rates for cholelithiasis in canadian women for each of the 8 years 1950, 55, 60...85 - Cohort analysis -

Figures are rates/1000

Age	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
1950 F*	0	0	0.004	0.021	0.035	0.097	0.21	0.22	
1960 F	0	0.0007	0.003	0.01	0.015	0.044	0.13	0.29	0.60
1970 F	0	0	0.002	0.003	0.009	0.023	0.053	0.17	0.41
1980 F	0	0	0	0	0.002	0.005	0.02	0.03	0.22

*For 1950, the denominator is that of the population in 1951

For 1950, the years 70-79 and 80+ are collapsed together in this table.

The highlighted diagonal gives the ordinates (mortality rates) for varying abscissa (years) for the cohort of females born in 1950. Similar analysis are performed for cohorts (grouped in 10 year intervals) of females born between 1880 and 1950 (as there was no reported mortality as of 1980 for women born after 1950).
With this data, the corresponding cohort contours plotting alternately death rate and log (death rate) vs age are shown in the figures below.

death rates and PYLL calculations over time show the difference in weighting attributed to young and old with each technique. Both show a gradual decrease in the rate or impact of mortality over time; however, this is more marked in the PYLL calculations where the mortality events which were already few have decreased further, and where a given event is weighed much more when occurring in a 50 year old female than an 80+ year old woman. The PYLL is usually more affected by changes occurring in younger subjects, and this is reflected here, however, the decrease in PYLL would be less dramatic if calculated up to age 85 for example. As most of the deaths occur in older age groups, even though their life expectancy would be less, the number of events would make it such that the overall PYLL trend would be less impressive, and thereby more comparable to the age adjusted rates which when calculated by the direct method are influenced by mortality in the older age groups. PYLL to life expectancy would be more useful in this context since this measure reflects the change in expected years of life saved over time. The small values of the PYLL displayed in appendix further show the limited impact of the disease with regards to mortality. This analysis suggests that, in Canada, cholelithiasis is a rare cause of death and most often kills elderly patients. The age adjusted mortality rates have decreased markedly over the past 35 years and probably represent better standards of medical care of the elderly (operative techniques, post operative care, etc...) although changes in the ICD classification have influenced these rates somewhat. No cohort or period effect is clearly identifiable confirming the importance of age. The PYLL analysis is limited by the "age limit" used for the computations and explains the possible discrepant rate of decrease over time when

comparing PYLL to age adjusted mortality. These data confirm that gallstone disease kills rarely, and only late on in life. The importance of this disease is nonetheless significant when considering the aging of the population and data relating to separation and morbidity. Any assessment of treatment alternatives for symptomatic gallstone disease therefore requires a thorough evaluation of other outcomes such as quality of life rather than mortality alone as a basis for comparative analysis. However disease specific measuring tools for cholelithiasis are lacking and require the use of more general quality of life assessment scales.

In summary, patients with gallstones can be divided into two prognostic groups: patients with silent and symptomatic gallbladder stones. No existing therapy seems to be indicated in individuals with silent gallstones due to associated benign outcome. Symptomatic gallstone patients, however, seem to need some form of intervention; in the past this has always meant surgery. We now examine the success of cholecystectomy, which remains today the gold standard in the treatment of cholelithiasis.

Treatment options

A comprehensive review of the different medical and surgical methods of treatment for cholelithiasis is beyond the scope of this thesis and recent excellent reviews exist in the literature (48,56). In the following section, we will concentrate on highlighting the important information required for the elaboration of a study designed to assess commonly available treatments for patients with symptomatic gallstones.

a. *The Surgical Treatment of Cholelithiasis*

Since the advent of laparoscopic cholecystectomy (LC) (6,7), 80-90% of all cholecystectomies are now performed using this "minimally invasive" approach (14,57). The bulk of the world literature on the treatment of gallstone disease, with trends according to population sub-groups, and long-term follow-ups however are still best discussed using experience gathered in the open cholecystectomy era. We will therefore first discuss open cholecystectomy, and then review the published data on LC.

Conventional Cholecystectomy: The mortality attributable to gallstone disease is small (6000 deaths per year in the USA (11)), and fell dramatically between 1950 and 1980 (58). This can only in part be explained by the availability and success of surgery. Taking a Swedish study as a case in point, a mortality decrease of 83% was paralleled by a steep decline in cholecystectomy rates (59). Despite geographic variations, this operation remains today the most commonly performed surgical procedure in the U.S.A. where it is carried out several times more often than in other areas such as in the United Kingdom without obvious benefit to the patient (60). The higher surgical rates may in fact increase overall gallstone disease mortality (60,61). In Britain 9 out of 10 subjects with gallstones do not have a cholecystectomy with national cholecystectomy rates of 70 to 79/100,000 (62). Women are two to three times more likely than men to have their stones removed (63). In Sweden the rate of cholecystectomy has decreased since 1969 (59), and in Canada it dropped by 20% between 1970 and 1976 (64). A recent study in centres with a special interest in gallstones reviewed the current status of

biliary tract surgery world wide (13). Overall mortality for cholecystectomy was 1.1% for the USA cohort, and 0.6% overall. When common duct exploration was added, however, the mortality rose to 5.8% in the USA, and 4.4% overall. More recent data have demonstrated no mortality in large series of patients (48). However, the continued drop in operative mortality has recently been offset by a further increase in cholecystectomy rates (65). The incidence of retained stones was 4.5%, and reached 10% in routine clinical practice as many surgeons performed selective, not systematic intraoperative cholangiography, and choledochoscopy when indicated in the open cholecystectomy era. This situation is even truer since the advent of LC. No iatrogenic bile duct damage was noted in an international study examining open cholecystectomy (13) (usually 0.3% [66]). These excellent overall results may have reflected increased expertise in the participating centers. With the treatment of acute cholecystitis by open surgery, the so called "early" cholecystectomy, the rate of misdiagnosis was at least 3% (67), and possibly higher (68,69). In follow-up, about 35-50% of patients are dissatisfied with their surgery, but although 5% complain of significant specific symptoms following cholecystectomy, most refer to nonspecific symptoms (70,71). Stricter operative indications could lower this number. Biliary sources for pain include retained common duct stones, and the poorly understood syndrome of biliary or sphincter of Oddi dyskinesia. As the population is aging, and the prevalence of cholelithiasis increases with age, we must specifically look at the published mortality of gallstone surgery in this group of patients. The overall elective cholecystectomy mortality rate is threefold higher in the elderly (72); morbidity is also higher due to sepsis (3-5% rate of wound

infections), cardiovascular complications, and venous thromboembolism. Published studies have reported cholecystectomy mortality rates of up to 2.5% in patients over 65 (sometimes as high as 3.3% [72]), compared to 0.1% in patients under 50 (73). Emergency cholecystectomy mortality rates were up to 16.7% versus 0.4% respectively. When common bile duct exploration is performed, mortality increases to as much as 29% in some series in patients over 70, as compared to 0.9% in patients under 50 (although some difference is attributable to whether a supra- or transduodenal approach is used [74]). The complications of gallstone disease are also more devastating in elderly patients because of concurrent medical diseases, or atypical presentations. In gallbladder empyema, fever or pain can be absent and this in part explains the high mortality of this entity in the aged (75). Age is a poor prognostic factor in acute pancreatitis (76), and a 9% mortality was associated with a first episode of acute pancreatitis in patients under 60, as opposed to a rate of 28% in those over 60 (77). Although the risk of developing complications from gallstone disease is not great, early detection and treatment of symptomatic patients appears indicated, especially in the elderly. Similar recommendations exist for selected patient subgroups such as diabetics (48,49).

Laparoscopic cholecystectomy: LC was initially practised in Europe (6,78) and soon thereafter in North America (7,14,15,48). The advantage of this procedure is its avoidance of a large incision slicing through skin and muscles of the right upper quadrant. Its theoretical advantages thus include a shortened hospital stay and total duration of convalescence owing to a decreased need for scarring and wound healing with less post-operative pain. This technique has now been practised in hundreds of thousands

of patients, and broad conclusions as to its safety and performance can now be put forward. LC is a very safe surgery with an operative morbidity lower than that of open cholecystectomy, especially with regards to pulmonary complications, including in the elderly (48,57, 65). An overall conversion rate of 5% from LC to an open surgery has remained remarkably stable from study to study (15,48,79-87). The risk of bile duct injury remains slightly higher than with the open surgery, yet decreases with operator experience, and is under 5/000 (15,48,79,88-95). As discussed above, the excellent operative mortality rates noted in the years of open cholecystectomy have further decreased by 33% in the LC era, yet have been offset in absolute terms by an unexplained 28% increase in cholecystectomy rates (65). The most important results, however, pertain to the durations of hospital stay and convalescence. Although uncontrolled data suggested a huge advantage of LC over open surgery, only recently have two randomized clinical trials definitively addressed this question with strikingly similar results (9,16). In the first published trial, the McGill Gallstone Treatment Group studied 62 patients and showed a statistically shorter duration of median hospital stay (3 vs 4 days, $P<0.001$), and median time to tolerance of a full diet (1.1 vs 1.7 days, $P<0.004$) in the LC group when compared to a control population undergoing mini-cholecystectomy (using the smallest possible abdominal incision, an optimal technique of the different open surgery alternatives available). Similar conclusions applied as to the results for duration of post-operative convalescence (11.9 vs 20.2 days, $P<0.04$). Using the Mantel-Cox statistic, the LC patient group showed a shorter duration of convalescence and more rapid return to normal activities (77% greater convalescence rate

for the LC group of patients, P=0,04). In addition, the post-operative use of narcotics was significantly less for LC patients. Both groups enjoyed a significant improvement of similar magnitude in quality of life assessments following surgery, yet this was achieved earlier in the LC group of patients. No significant between group differences in early morbidity or mortality rates were noted, although the number of patients studied was small.

Laparoscopic cholecystectomy is also indicated in patients with acute gallstone pancreatitis (94), and has become the treatment of choice for acute cholecystitis (95). The management of patients with symptomatic gallbladder stones and suspected common bile duct stones has been extremely controversial since the introduction of LC. This issue, however, is beyond the scope of this thesis, and will not be further discussed.

The presented data, particularly those of the randomized trials, have confirmed the adoption of LC as the new gold standard surgical treatment for gallstone disease. However, LC still requires, an operation and a general anaesthetic, and patients have sought medical alternatives. These are discussed below.

b. *The medical treatment of Cholelithiasis*

Oral bile acid dissolution: Oral compounds which act as cholesterol solvents have clinically been used to dissolve gallbladder stones. These have included chenodeoxycholic acid (CDCA), and ursodeoxycholic acid (UDCA) (96-107). The former, in older trials was shown to have a significantly high rate of side-effects including hypercholesterolemia (10-20 mg/dl rise in LDL), elevated aminotransferases

(30%), and diarrhea (30-60%) with only a modest overall stone dissolution rate (99,102,103,106,107,108). UDCA, is a much safer agent which, in a recent meta analysis, displayed 40% overall stone dissolution and disappearance rate (109). This success rate increases to 80% with proper patient selection as best results are seen in patients with small, floating stones amidst a functional gallbladder (109). CDCA and UDCA may also be used prophylactically in special clinical circumstances when gallstone formation is anticipated, such as in rapid and significant weight loss (110), or to prevent stone recurrence (111). Although there some evidence to suggest improvement in both gallstone related and non specific symptoms with oral bile acid treatment, the effect of UDCA or CDCA remains controversial in the absence of controlled trials (105-107,112-113).

Gallbladder stone lithotripsy: Extracorporeal shock wave lithotripsy was initially applied to urological stones with impressive results (114). Its subsequent use in fragmenting gallstones has enjoyed less success but nonetheless became widespread in Europe in the early 1990's (5). Yet a more rigorous assessment of this technique remained lacking. Three major types of lithotripter generators exist on the market (detailed in reference 5), all of which generate a shock wave (or modified ultrasonic wave) outside the body which is focused on the stones in the patient's body (5). Depending in part on the type of lithotripter generator, stones are fragmented in vitro in over 90% of patients, although in vitro fragmentation to small fragments is achieved in only 30-40% (115,116). The outcome of lithotripsy has usually been assessed in terms of results on stones themselves (115-119), while other issues concerning patients

determinants have remained largely unexplored; these may include body mass (120) and gallbladder size (121). Animal safety studies (119,122,123), and human pathological data (124) have confirmed that trifle or no tissue damage occurs, as long as the shock wave path avoids the lung bases (125). The eligibility criteria adopted by most clinical studies published to date followed the initial Münich recommendations (126), which restrict the technique to patients with functioning gallbladders, with not more than three stones, a maximum stone diameter of 30 mm or less and with no visible X-ray calcifications of the stone. This selection limits the application of cholelithotripsy to only about 10-20% (127) of all patients presenting for cholecystectomy, although the actual patient denominator is difficult to assess because of referral patterns (128). Despite sporadic attempts at increasing inclusion criteria (129-133), a recent large cohort of nearly 700 treated patients confirmed the need for such rigorous patient selection at this time (134). Nonetheless, in the subgroup of patients with small and few gallbladder stones, fragmentation has been achieved in 70-90% of cases (5). Satisfactory fragmentation (defined by the persistence of fragments of no more than 5 mm (5)) seems to approximate 40-60%, although heterogeneity in reporting makes conclusions somewhat uncertain (5,126,128,135-150). Electrohydraulic generators have on average required fewer sessions than the other two generator types to achieve this endpoint (5). It would appear that the shock waves themselves are safe though they cause reversible enzymatic rises (126,135-150) not usually found with the second generation machines (5). These include leucocytosis, as well as rises in aminotransferases, alkaline phosphatase, amylase which all return to normal within the month following lithotripsy. Recent data from the

urological literature suggests that the late development of systemic hypertension might occur, but the epidemiological evidence for this association, let alone the proof of causation, is very weak at present (5). One major disadvantage of the early machines was the need for general or epidural anaesthesia (126). With the advent of second generation lithotripters, there is only a need for intravenous analgesia (the electrohydraulic generators), or nothing at all (the piezoelectric and electromagnetic generators), and outpatient treatments are the norm (139,141-150). But the decrease in pain associated with treatment has been paralleled by a drop in fragmentation efficacy in the case of the electrohydraulic generators (5, 150. Groups which have treated all stones without restrictions report accordingly variably lower fragmentation rates (129-134,140). Although in vitro data suggest the basis for a possible expansion of selection criteria on the basis of CT scan appearance (116), small, solitary, uncalcified stones are the most likely to fragment satisfactorily, and will do so 70% of the time (5). The resulting fragments are then treated by oral bile acids, which have been shown to accelerate the dissolution rate (151). The morbidity due to this therapy is minimal and consists of diarrhoea in 4-10% of patients when UDCA is used alone or with CDCA (5). Despite the safe use of UDCA in some pregant women (108), animal studies with CDCA administration could not completely rule out possible teratogenic effects (152). Of the patients in whom satisfactory fragmentation has been achieved, and who take bile acids, 90% will be stone free after a year (5). Overall, initial results suggested that 90% of patients presenting with small stones could be expected to be free of any after 18 months, especially if they were solitary. For unclear reasons, more recent reports have yielded

markedly lower stone disappearance rates (142,144,148,153,154). Some investigators have put forward possible reasons for these observed discrepancies along with suggestions to improve results (149). The former include patient selection and operator bias, as well as the use of different machines and settings, in addition to bile acid dissolution. Despite the abundance of data, factors other than stone burden which determine the effectiveness of stone dissolution following fragmentation remain unclear. Most research has focused on gallbladder volume and contractility (155-161). Most protocols now call for the administration of adjuvant oral bile acid dissolution until three months following the ultrasonographic disappearance of any debris in the gallbladder. Randomized controlled trials have now shown that adjuvant dissolution therapy is beneficial compared to placebo (142,143) confirming the aforementioned in vitro data (151). During stone dissolution, complications attributable to the persistence of fragments are few and include pancreatitis (which averages 1%), cholecystitis (which is reported in 2-6% of patients), and biliary colic (which occurs in one third of patients (5). These results also signify that up to 66% of patients have no further episodes of colic following cholelithotripsy in the short term follow-up. There are limited data which all suggest lower than anticipated recurrence rates in both the short (11%±3% at 2 years) and long term recurrence (31%±7% at 5 years [162-166]). These are likely related to the inclusion of mostly patients with solitary stones - a subgroup of patients known to exhibit lower stone recurrence (102). Investigators are now examining possible pharmacologic approaches to decrease stone recurrence, such as the use of aspirin, so far with limited success (167). Others have attempted to combine ESWL with LC (168) or methyl-tert-

butyl ether (169). Determinants of stone recurrence also remain unclear, although gallbladder contractility may play a role (155-161).

Despite the impressive amount of literature and research which has been published so far on this new technology, only two groups have published randomized controlled studies comparing gallstone lithotripsy to cholecystectomy, in both cases the open surgery (153,154). In the first study, 163 patients were randomized to receive open cholecystectomy or ESWL (153). Both treatments gave significant health gains with regards to episodes of biliary pain, improved perceived health status, and symptom relief. However, few between group differences were found. The second study included 49 patients and found significant differences in biliary colic disappearance (90.9% for surgery versus 45.4% for ESWL after 3 months) (154). However, no differences in gastrointestinal symptoms were noted from 6 months on, up to 18 months follow-up. The authors concluded the superiority of surgery. Others have confirmed the disappearance of biliary colic, but less so non specific symptoms following successful lithotripsy (170).

When interpreting the results of the two randomized studies, one must bear in mind that the lithotripters used may not have been optimal due to suboptimal energy delivery, and some of the endpoints used for the study included nonspecific symptoms that are now known to be unrelated to gallstone disease. Finally, both studies compared the efficacy of ESWL to a surgical procedure which is no longer the gold standard.

Published information relating to the cost of treating gallstones

There have been many studies reporting the costs of different treatments for

gallstone disease. However, many fall well short of addressing the six analytic principles suggested to ensure the adequacy of statistical methods, the correctness of the assumptions, and the appropriateness of the interpretation of results (171). These include (1) an explicit statement of the perspective for the analysis, (2) an explicit description of the benefits of the technology, (3) the types of costs considered, (4) adjustment of costs using discounting to account for differential timing, (5) the use of sensitivity analysis, and (6) a summary measure should be used (cost-benefit or cost-effectiveness), expressed in marginal costs.

One study, using decision analysis, suggested the superior cost-effectiveness for ursodeoxycholic acid treatment over elective open cholecystectomy in men over 64 and women over 69 because of the increased operative risk in this group (172).

A number of studies have compared the cost-effectiveness of LC to the open alternative suggesting the superiority of LC when using both decision modelling (173), and retrospective collection of effectiveness including both direct and indirect cost data (174).

An early study, using American charges and direct cost analysis, suggested that ESWL would be too expensive to become a viable treatment alternative (174). Authors have compared the cost-effectiveness of ESWL to open surgery arriving at different conclusions. A prospective cost analysis of 76 patients suggested less costs attributable to in-patient ESWL (175). However, other comparative studies having collected data prospectively from non-matched patient groups found in-patient ESWL to be more expensive than open cholecystectomy (176), including one unpublished Canadian study

(Krueger et al, personal communication). Using a Markov decision process and four possible treatment strategies, one group confirmed the correctness of an expectant approach for asymptomatic gallstone bearers (177). These investigators also suggested that ESWL was a feasible therapeutic alternative where a low success rate of lithotripsy would raise its direct costs above those of open cholecystectomy but leave total costs of both strategies in the same order of magnitude (177).

The randomized trial comparing open cholecystectomy to ESWL discussed previously showed that ESWL was "at least as cost-effective" as surgery for patients with a small gallstone burden (153).

Using a societal perspective and a Markov approach, investigators demonstrated the increased cost-utility of ESWL over open surgery (178). A thorough decision analysis, arguably the best published of its kind performed by Bass et al., suggested that the resulting marginal cost-effectiveness of ESWL versus open cholecystectomy is $216,000 of extra charges per year of life gained with ESWL (179). Adjusting for effects of morbidity on quality of life, ESWL was projected to have slightly better quality-adjusted survival than open cholecystectomy for the small subset of patients with one stone (by 8 to 43 days at 5 years) but not for young patients with multiple stones (179). However, this analysis focused primarily on direct, not indirect costs and on mortality and significant morbidity, not other quality of life considerations - both key issues when examining the impact of gallstone disease (4).

Two more recent, well performed decision analyses examined open cholecystectomy, LC, and ESWL, or LC only (180,181). The two studies arrived at opposite conclusions with

regards to the per-case cost of LC versus ESWL due to varying assumptions.

The aforementioned results show the confusion which exists around any final results interpretation, in part due to the lack of clinically relevant outcomes or utility data comparing the different alternatives.

Beyond the aforementioned cost considerations lie the "real life" issues of technology diffusion and modification of practice patterns (8). These need also be considered when examining the impact of the new therapeutic biliary technologies on the Health Care System as they may alter, sometimes unpredictably, the cost-effectiveness assumptions drawn from scientific studies for any proven technology. As an example, since the advent of LC, the cholecystectomy rate has risen by 17% in Canada, and 24% in Australia (182), while in the USA, it has soared by 28-59% (65,183), markedly more than for other "control" surgical procedures over the same time period (183). Consequently, the overall "benefits" brought to individual patients with LC has also resulted in a staggering cost increase to the Health Care System, a finding which was not anticipated from existing cost-effectiveness or cost-utility studies.

Table B: Summary of the quality of evidence for therapeutic trials for cholelithiasis reviewed by reference number (excluding articles using modelling only).

Modality of treatment assessed	Quality of evidence
LC: 6,7,15,78,83,85,86,89,81,82,84,87,88, 91,92,93,94,95	case series
79,80	cohort studies
ESWL: 12,117,119,126-141,143,144,146-150 155,157,159,161,162,163,164,165,166,170	cohort studies
142	RCT (vs placebo)
OC: 13,39,67,68,69	case series
44,70,71,72,73,74	cohort studies
62	prevalence studies
OBA: 97,99,100,103,105, 106,107,110,111	cohort studies
54,102	RCT (vs placebo)
ESWL and MTBE: 169	cohort studies
LC and ESWL: 168	case series
LC vs OC: 9,16	RCT
65	prevalence studies
OC vs ESWL: 153,154	RCT
LC vs ESWL: 10	RCT
145	comparison of cohorts

Open cholecystectomy = OC

Laparoscopic cholecystectomy = LC

Gallbladder stone shock wave lithotripsy = ESWL

Oral bile acid = OBA

Randomized controlled trial = RCT

THE RANDOMIZED CONTROLLED TRIAL

STUDY JUSTIFICATION

The same physician and patient pressures which brought on ESWL and permitted its rapid, premature diffusion in Europe have been responsible for its inability to undergo a proper evaluation in North America with the advent of LC (8,87). This temporal sequence of events, coupled to inherent difficulties in carrying out clinical trials comparing medical to surgical therapy (8), have resulted in a paucity of controlled data contrasting ESWL to open cholecystectomy, let alone LC - the new gold standard treatment of symptomatic cholelithiasis (9,16,57). Furthermore, there exist very few clinical outcomes data relevant to patients with gallstone disease which would permit an adequate characterization of effectiveness.

We therefore proposed, undertook, and completed the only randomized controlled trial in the world comparing ESWL to LC. Its methodology was designed to address pertinent outcomes of effectiveness and cost which better identify the role of ESWL, and permit more appropriate counselling of patients and a resulting tailored treatment selection.

STUDY OBJECTIVES AND HYPOTHESIS

(1)To compare the efficacy of two alternative treatments with respect to total duration of disability, and quality of life.

(2) To determine the relevant direct costs attributable to each treatment.

(3) To determine the appropriate cost-effectiveness attributable to each technique.

The primary study hypothesis was that, in the short-term, ESWL would result in a briefer duration of hospital stay, convalescence, a better quality of life, and cheaper care as compared to LC. However, these outcomes would favour more LC in the long-term (beyond the first 1-3 months) with repeated attacks of biliary colic (due to stone persistence or recurrence), and cross-overs amongst patients randomized to ESWL.

METHODS

Patient selection

From September 1990 to August 1992, patients were recruited from four University Hospitals in Montreal. All symptomatic patients aged 16 to 85, having experienced, within the last 6 months, at least one episode of right upper quadrant or epigastric pain lasting at least 30 minutes (pain clinically thought to be compatible with biliary colic), with ultrasound proven cholelithiasis, who were judged fit for elective cholecystectomy, were eligible for entry into the trial. Because of the requirements for ESWL, included patients needed to have no more than three non calcified gallbladder stones, each measuring anywhere from 6 to 30 mm amidst a gallbladder which opacified on oral cholecystography. Because of the requirements for LC, patients who were unfit for general anaesthesia, or who had previously undergone upper abdominal surgery were excluded. Other reasons for exclusion were pregnancy, advanced liver disease, acute cholecystitis, coagulation abnormalities, the

presence of a pacemaker or abnormal atrioventricular conduction, an abdominal vascular aneurysm, a pneumonic consolidation on chest x-ray, or any patient not wishing to participate in random allocation to either treatment group. An additional reason for exclusion was the pre-operative suspicion of a common bile duct stone, based on historical, biochemical, or ultrasonographic abnormalities (184). Written informed consent was obtained from all patients prior to randomization. The study protocol was approved by Institutional Review Boards at each participating institution.

Treatment and follow-up protocols

Following an initial visit to one of the study clinics, eligible and consenting patients were stratified according to age (greater or less than age 55) and randomized to either the ESWL or LC group. Pre- and post-treatment data were collected by study nurses, who did not directly participate in the care of the patients but were not blinded with respect to treatment assignment. All LC patients received single dose antibiotic prophylaxis at the time of anaesthesia. Each participating surgeon (6 in all) had performed at least 30 laparoscopic cholecystectomies before operating on their first study patient. LC was performed under general anaesthesia, using either European or North American trocar positions (9).

All ESWL patients were started on ursodeoxycholic acid (10 mg/kg/ day) as a single nighttime dose within the two weeks prior to lithotripsy (126). The patients (barring the development of side effects, or discontinuation of contraception in fertile women) remained on the oral bile acid until stone disappearance or the end of the

study period. Compliance was monitored by pill count at the follow-up visits with the patients bringing in their pill containers. In addition, a daily diary filled out by each patient included a pill count tabulation which was reviewed at each visit. All lithotripsy treatment sessions were carried out on an out-patient basis with no or minimal intravenous sedation using an electromagnetic generator, the Lithostar^{+} machine (Siemens), located at the Royal Victoria Hospital. Positioning and targeting was carried out as described previously (138), and ultrasonographic control of fragmentation was carried out every 1000-2000 shocks with frequent repositioning performed with the in-line probe as needed. Lithotripsy was carried out until satisfactory fragmentation was achieved (only fragments 5 mm or less remained) or until a total of 4000 shock waves with a capacitor setting of 16-19 kV for a power level approximating 6 unless a complication forced premature termination. Sessions were usually repeated every one to 4 weeks up to a total of three sessions or until satisfactory fragmentation. Following the last lithotripsy treatment session, all ESWL patients underwent ultrasound follow-ups at 1 week and three monthly thereafter.

All patients were seen in follow-up by the study nurses in specialized gallbladder clinics at 7-10 days, 1 month, and 3 month intervals following treatment. In addition, the LC patients were also assessed in the treating surgeon's private office within the month following surgery.

Patient assessments

Pre-treatment data included patient demographics, history and physical

findings, as well as biochemical and ultrasonographic results for all patients. The severity of co-morbid conditions was categorized by using the American Society of Anaesthesiologists (ASA) scoring system (185). Additional parameters examined were the pre-treatment duration since the first episode of biliary colic, and the frequency of attacks thereafter, Quetelet's index of body mass (186), ultrasound measured gallstone and resting gallbladder volumes (187) and gallbladder emptying on HIDA nuclear scanning which is measured by the gallbladder ejection fraction (188) which were performed after starting ursodeoxycholic acid, the computerized tomographic stone appearance and the stone density distribution index of each patient's stones (in Hounsfield Units [HU]) as described previously (116).

Measurements of outcome

Because of the nature of this clinical trial which compares a medical to a surgical treatment, not all outcome measures are common to both treatment arms. This is especially true as stone fragmentation and dissolution is contrasted to the surgical ablation of the gallbladder. However, the chosen outcomes are all of clinical interest, and reflect the impact of the disease and its treatment on the study patients' activities.

Outcomes for LC patients were the length of hospital stay, the time to full convalescence, the total number of days of usual activities lost because of recurrent biliary colic due to an unsuspected retained stone or a post-cholecystectomy biliary syndrome. The number of days in hospital was counted from the day of admission (on

the day prior to surgery in all cases) up to and excluding the day of discharge from hospital (for subsequent costing purposes). Convalescence was defined as complete, when a patient could perform all usual home activities, if unemployed, or full usual duties at the work place if employed.

Outcome measures for ESWL patients included duration of convalescence post treatment, and the total number of days of usual activities lost because of the treatment (which when uncomplicated was delivered in an outpatient setting), or biliary colic recurrence and any possible complication of persistent or recurrent cholelithiasis, or unsuspected choledocholithiasis following treatment. Significant biliary colic was defined as nay episode of colic requiring the use of medications or a visit to a physician which, in both cases, required time away from usual activities (grades 3 and 4 on a 1-4 scale noted on the daily diaries). As for the LC group, these events were determined by tabulating data collected from the patients three-monthly visits and a patient diary sheet filled out at home during the three month follow-up intervals.

The major outcome of the study was the "duration of disability" for all patients. This endpoint was measurable and directly comparable between both groups. It takes into consideration the acute recurrent nature of biliary colic, the treatment and complications of gallstone disease and its varying impact on daily life - the most relevant consideration for patients afflicted with symptomatic cholelithiasis. The duration of disability reflects for ESWL patients the total sum of days away from daily activities attributable to the work-up and treatment (all but the CT and nuclear

scans which were solely performed for secondary study purposes), post-treatment convalescence, colic recurrence, as well as regular follow-up (not related solely to study purposes). In addition are counted the days away from daily activities attributable to a complication of gallstone disease or its treatment. A similar duration of disability was tabulated for all LC patients which included the hospital stay. Significant biliary colic was defined as any episode of colic which required patients to discontinue their usual activities at home or work (where applicable), and if need be, seek medical help. Fragment disappearance was defined in the lithotripsy group as two successive ultrasound examinations showing no residual debris in the gallbladder (5), and stone recurrence as the reappearance of stones following disappearance (5).

Secondary outcomes included post-operative pain and quality of life. Post-operative pain was assessed by administering the McGill pain questionnaire (189-193) within the first 24 hours following surgery, or prior to discharge home following lithotripsy. This index of pain has been shown to be sensitive in patients following cholecystectomy (9). Quality of life measurements were taken pre-treatment, and post-treatment at one and three months, and at six-monthly intervals thereafter. The questionnaires were filled out by the patients after having received standardized instructions from the study nurses. We used three different instruments to measure quality of life. The Nottingham Health Profile Questionnaire (NHPQ) is a general quality of life index (194-198). We also used a recently validated index of quality of life for patients undergoing gastrointestinal surgery (which we will refer to as the German Gastrointestinal Quality of Life Questionnaire score or GGQLQS [199])

which is available in both english and german versions. This questionnaire is both general and specific, and has been found to be sensitive to change in patients post-cholecystectomy (9). Lastly, a Visual Analogue Scale representing overall quality of life was also used as described previously in a similar group of patients (9).

Secondary outcomes specific to LC patients included the conversion rate to open cholecystectomy, and post-operative days to full diet. Mortality and morbidity are important outcomes and were recorded, but were of limited significance in this trial given the anticipated small sample size and the limited time of follow-up. Peri-operative complications such as atelectasis, wound infection, venous thrombosis, and pulmonary embolism were nonetheless sought. Possible post-treatment morbid events to be recorded in both groups were retained stone rates, the incidences of recurrent biliary colic, pancreatitis, ascending cholangitis (and the need for an endoscopic retrograde cholangio-pancreatography [ERCP] with or without an endoscopic sphincterotomy).

In the ESWL group, additional endpoints included acute cholecystitis due to cystic duct or Hartmann's pouch obstruction, and the need for cholecystectomy - ie cross-over, because of recurrent colic or cholecystitis. Stone disappearance and subsequent stone recurrence rates were analyzed. Possible prognosticators of stone fragmentation were also assessed including the stone density distribution index, as well as the gallbladder volume at the time of lithotripsy.

The collection and calculation of cost data

Only direct costs were tabulated as the aim of this part of the study was to quantify the total direct costs to the health care system of each of the two strategies for management of symptomatic cholelithiasis. Only the capital costs of specialized equipment specific to the interventions at issue were included. The general approach taken was to delineate the steps involved in each management strategy, estimate the frequency with which each occurs and multiply this by the estimated average cost of that step. Each average cost was estimated as the product of the average volume of resource use and the corresponding unit costs. Reasonable upper and lower bounds were established by considering the most and least expensive instances. For the capital costs that were included, bounds were set by considering lowest and maximum levels of use of the equipment. The average resource use at each step was estimated from the data collected in the trial's data abstraction forms which included exhaustive accounting of all resources used. Nevertheless, the clinic and hospital charts of all trial participants were also audited to verify resource use. Any discrepancies were resolved in favour of the permanent medical record. The actual resources consumed were counted rather than those that might have been, or ought to have been used. No attempt was made to judge the necessity or effectiveness of the resource use that was found. All resource consumption with primarily a research purpose was excluded. Where there was doubt, the resource use was considered part of clinical practice rather than research.

All data pertained to activities carried out at the study centres. Although there

were no data on any services that may have been provided at other institutions, it is unlikely that they amounted to much given the close follow-up inherent in the clinical trial. To the extent that there was uncounted resource use, it most likely occured prior to patients' enrolment in the trial and represented mainly duplication of diagnostic tests such as abdominal ultrasound.

Estimation of unit costs for each test, technical and medical components were estimated separately. All estimates were in 1993 Canadian dollars. The cost of the technical component was estimated from the data provided by the Management Information Systems Group (MIS). Operating on a national level, this group has developed a workload measurement system that periodically updates all relevant data (diagnostic and therapeutic services, hospital personnel and administration) to ensure comparability and to encourage standardization. For all tests, the MIS system already provides an estimate of the fixed cost (technician time, equipment, etc.) and of the variable cost (laboratory supplies, etc.). These have been shown to be valid and stable for tertiary care institutions. For tests not yet covered, an estimate of the cost was made in collaboration with the MIS representative at one of the participating institutions (the Royal Victoria Hospital or RVH). To the best of our assessment, these estimates also appeared valid, and stable. They would be generalizable to similar tertiary care institutions in the Canadian Health care system. The medical component was estimated in consultation with the directors of each laboratory; it varied according to the manner in which each laboratory bills the organization which pays for the provincial universal health care (la Régie de l'assurance maladie du

Québec or RAMQ).

The professional fees for each act were obtained from the specialists' manual and the Hospital Insurance Manual of the RAMQ. In addition, as all acts took place in a hospital centre and the office costs are borne by the hospital, a hospital component estimated by Financial Services of the RVH, in consultation with the appropriate clinical services, was added to each medical act.

The unit costs of medications dispensed by the hospital were estimated from information obtained from the MIS representative at the RVH. The cost of a day of admission to a hospital ward was obtained from Financial Services of the RVH. It covers the average cost of pharmacy, administration, housekeeping, security, laundry, meals, plant operations, communication, transportation, medical records and plant and equipment maintenance. The cost per hour of use of the operating theatre, recovery room and per diem in the intensive care unit were also obtained from Financial Services of the RVH.

The unit costs of the specialized equipment required for lithotripsy and laparoscopic surgery (considering equal use of disposable and non-disposable trocars) were determined considering the capital cost of the equipment amortized over 7 years, the annual costs of service, replacement heads and disposables (for the lithotripter), all divided by the yearly number of treated patients.

The marginal cost-effectiveness ratios were calculated (171), using incremental costs as numerator, and incremental durations of disability as denominator. A sensitivity analysis was performed varying in turn the cost estimates (or assumptions

used to reach these), and the effectiveness estimates.

Statistical methods

All results were analyzed according to the intention to treat principle, thus cross-overs were included in the group to which they had originally been assigned. Continuous descriptive variables are expressed as mean ± standard deviation. Between group differences for continuous variables were assessed for statistical significance by the use of Student's t-test and the nonparametric Wilcoxon's rank sum test. The Chi-square statistic or Fisher's exact test were used for comparison of categorical variables. Changes from baseline values for the quality of life measures were evaluated using paired tests whereas between group differences with respect to these changes were assessed by non paired procedures. For time to complete convalescence (LC), the time to significant biliary colic (ESWL), and the stone disappearance rate (ESWL) the Kaplan-Meier method was used to construct life tables.

RESULTS

Patient population

Over a 24 month period, 528 patients were assessed in the four gallstone clinics. A total of 468 patients (89% of all patients assessed, mean age 51.8±15.3 years, 72% female) were excluded from the study. A detailed breakdown of the reasons for exclusion is shown in table 1 with 392 (84%) patients excluded because

Table 1: Reasons for patient exclusions

468 patients excluded (mean age 51.8 ± 15.3 years, 72% female)
113 (24%) asymptomatic gallbladder stones
171 (37%) more than three gallbladder stones
19 (4%) calcified gallbladder stones
15 (3%) non-visualized gallbladder on OCG
8 (2%) no gallbladder stones found on ultrasound
7 (2%) acute cholecystitis
4 (1%) stones diameter outside the 6-30mm range
55 (12%) miscellaneous exclusions*
76 (12%) chose no treatment or refused participation

OCG=oral cholecystography

* Miscellaneous reasons included: age>85, ineligibility for laparoscopic cholecystectomy due to significant co-morbid diseases or previous upper abdominal surgery.

they were found not to be candidates for LC and/or ESWL. In only 76 (16%) patients was refusal to partake in the trial the sole criterium for exclusion. Of the 60 patients included in the study, 35 were randomized to ESWL, and 25 to LC. Three patients in the ESWL group were not treated (one patient refused ESWL, one patient was diagnosed with Takayasu's arteritis following randomization and prior to ESWL treatment, and a third patient was lost to follow-up prior to treatment). All patients in the LC group had surgery.

Baseline values

There were no clinically or statistically significant differences in pre-treatment population characteristics between both groups with regards to age, gender distribution, duration since initial onset or most recent episode of biliary colic symptoms, Quetelet index, ASA score, stone number, size or total stone burden. The baseline quality of life assessments including NHPQ, GGQLS, and VAS scores were also similar. All baseline values for each treatment group are shown in table 2.

Immediate results

The 32 ESWL patients were started on a mean nightly ursodeoxycholic acid dose of 602±125 mg, and averaged 1.75±0.84 treatment sessions (0.70±0.48 hrs in duration) resulting in a satisfactory fragmentation rate of 78% (mean total: 3450±867 shocks). The mean gallbladder volume at the first ESWL session averaged 12240±29702 mm^3. In the ESWL group, the mean fentanyl and midazolam doses

Table 2: Pre-treatment characteristics of included patients

	ESWL (N=35)	LC (N=25)
Age	51.7±13.3 yrs	47.4±14.3 yrs
Female gender	71%	80%
Time since initial symptoms	28.1±42.6 wks	15.1±18.1 wks
Time since last symptoms	1.7±2.5 wks	0.8±0.9 wks
Quetelet Index (kg/m^2)	24.6±4.7	26.8±3.9
ASA score > 1	24%	23%
Stone number	1.3±0.6	1.4±0.5
Diameter of largest stone	13.4±6.8 mm	12.2±10.4 mm
Total stone burden	16.4±6.6 mm	19.4±6.6 mm
Baseline quality of life scores		
NHPQ	8.4±7	7.7±5.7
GGSQLS	64.2±17.8	61.8±16.1
VAS	7.0±2.4	6.6±3.0

ASA score = Co-morbid disease scale (The American Society of Anaesthesiologists' classification where 1=healthy to 5=moribund)

NHPQ = Nottingham Health Profile Questionnaire

GGSQLS = German Gastrointestinal Surgical Quality of Life Scale

VAS = Visual analogue scale

Total stone burden = Sum of measured stone diameters per patient

There were no clinically or statistically significant differences in baseline characteristics between both groups.

used were 88±67 μgm, and 1.4±1 mg respectively. The gallbladder could not be visualized at nuclear scintigraphy in 5 ESWL patients. In the remaining 27, the mean gallbladder ejection fraction was 40±26%. The mean stone density distribution index for the stones of all ESWL patients was 40±37 HU. No predictors of satisfactory fragmentation at ESWL were found amongst the different variables studied (total stone burden, gallbladder volume, SDD index, or Quetelet Index).

The 25 LC patients stayed in hospital for 2.8±1.5 days and had returned to eating a full diet within 0.6±2 days following surgery. There were no significant differences in immediate post-treatment McGill Pain Questionnaire scores between both groups (ESWL: 15.7±9.5 versus LC: 20.6±14.4, $P>0.05$). No LC patients needed to be converted to open cholecystectomy.

Procedure related complications included: 1 (4%) minor intra-operative haemorrhage (estimated blood loss under 500cc, the patient did not require a blood transfusion) in the LC group. One (3%) ESWL session was stopped prematurely due to transient, self-limited pain after 3042 shocks, and ESWL sessions were cancelled in 2 (6%) patients because of inability to target the stone(s)/fragment(s) adequately.

Results of follow-up

The ESWL patients were followed for a total of 426 patient-months with a median of 15 months (range 1-24 months), and LC patients for 250 patient-months, with a median of 18 months (range 1-21 months). Overall compliance to ursodeoxychoic acid was 66% for all ESWL patients. Complete stone disappearance

was achieved in only 38% of ESWL patients. The life table analysis plotting stone disappearance following ESWL in time is shown in figure 1. The gallbladder ejection fraction prior to ESWL was not found to be a predictor of fragment disappearance post-ESWL (47±25% for patients with stone disappearance vs 36%±16% for those without, P=0.25). An asymptomatic stone recurrence was noted in 1 (3%) ESWL patient 18 months following stone disappearance.

The duration of convalescence averaged 0.5±1.2 days in the ESWL group, and 18.2±16.8 days in the LC group. The life table analysis of post-LC convalescence is shown in figure 2.

Recurrent biliary colic was experienced by 22 (68%) ESWL patients within 3.4±3.6 months and one (4%) LC patient 15 months following surgery. Significant biliary colic was noted in 6 (18%) ESWL within 2.8±4.9 months of treatment. Five of six (83%) patients experienced significant biliary colic in the first month following ESWL in contrast to 12 of 22 (54%) who experienced milder colic over the same duration post-ESWL. The proportion of patients experiencing significant recurrent colic was thus significantly greater in the first month following ESWL as compared to any time thereafter (P=0.01). The sixth patient had significant colic in the twelfth month of follow-up. Biliary colic was also significant in the one (4%) LC patient with symptom recurrence. Time off due to colic recurrence averaged 7.6±15 days in the ESWL group. The sole LC patient required 6 days to recover from her bout of recurrent colic which occurred 15 months following surgery. The life table analysis of recurrent biliary colic following ESWL is shown in figure 3. Recurrent bouts of

Figure 1: Life table analysis of stone disappearance following ESWL.

STONE DISAPPEARANCE FOLLOWING LITHOTRIPSY

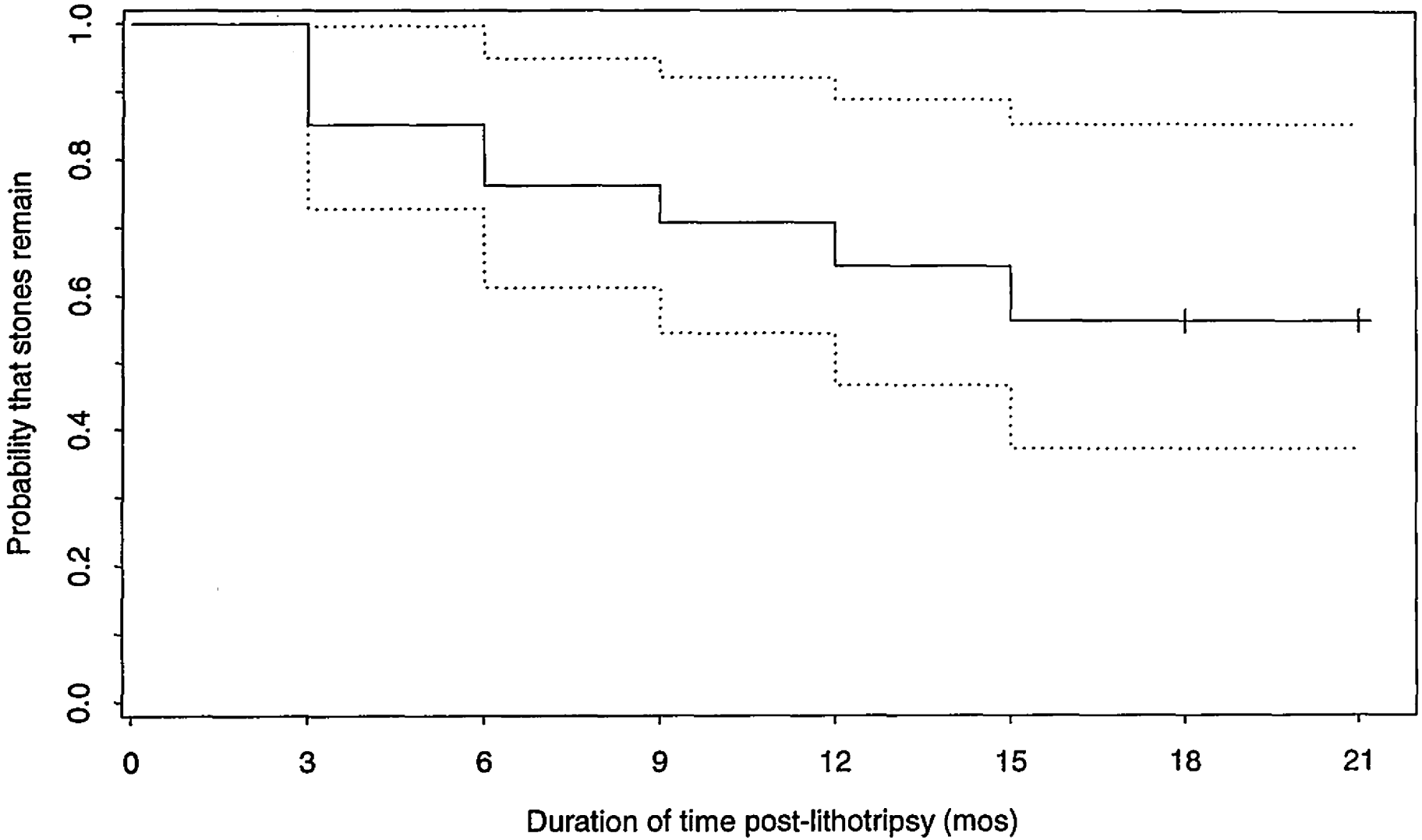


Figure 2: Life table analysis of post-operative convalescence following LC.

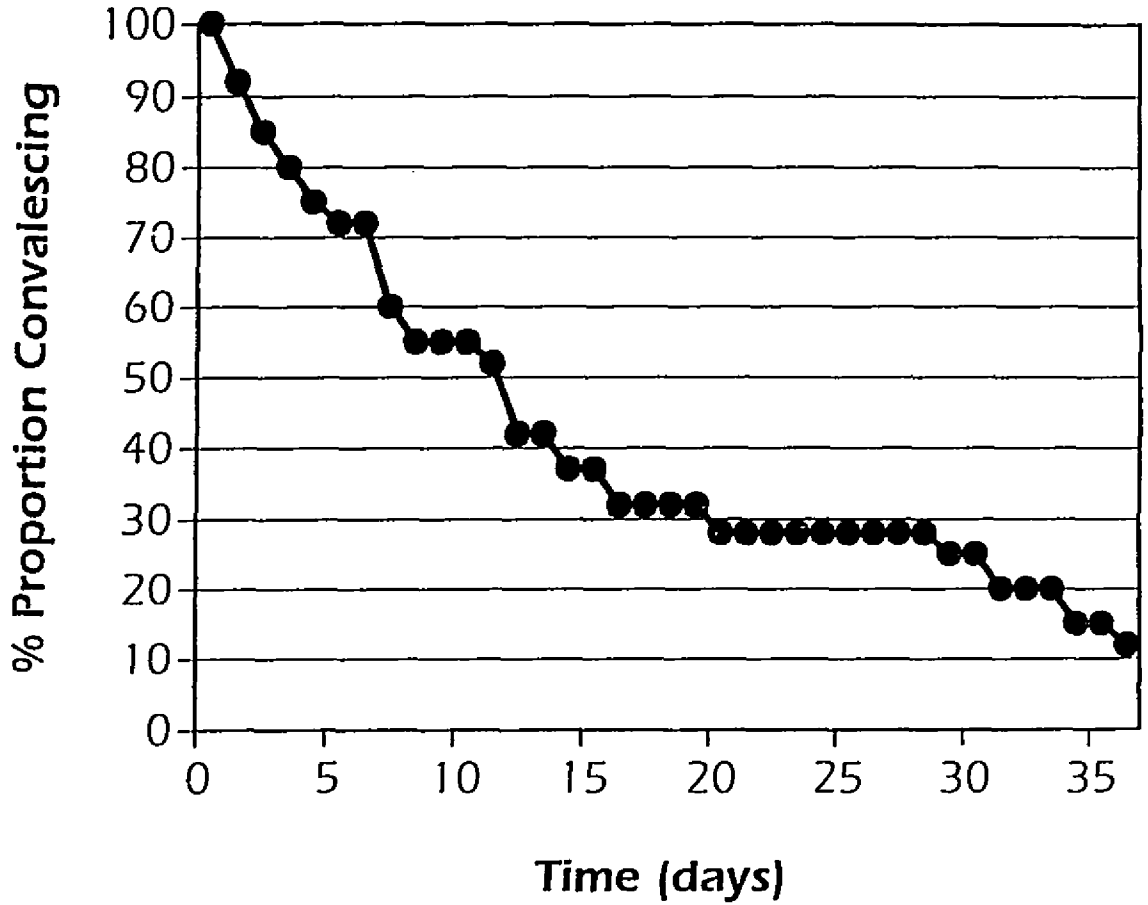
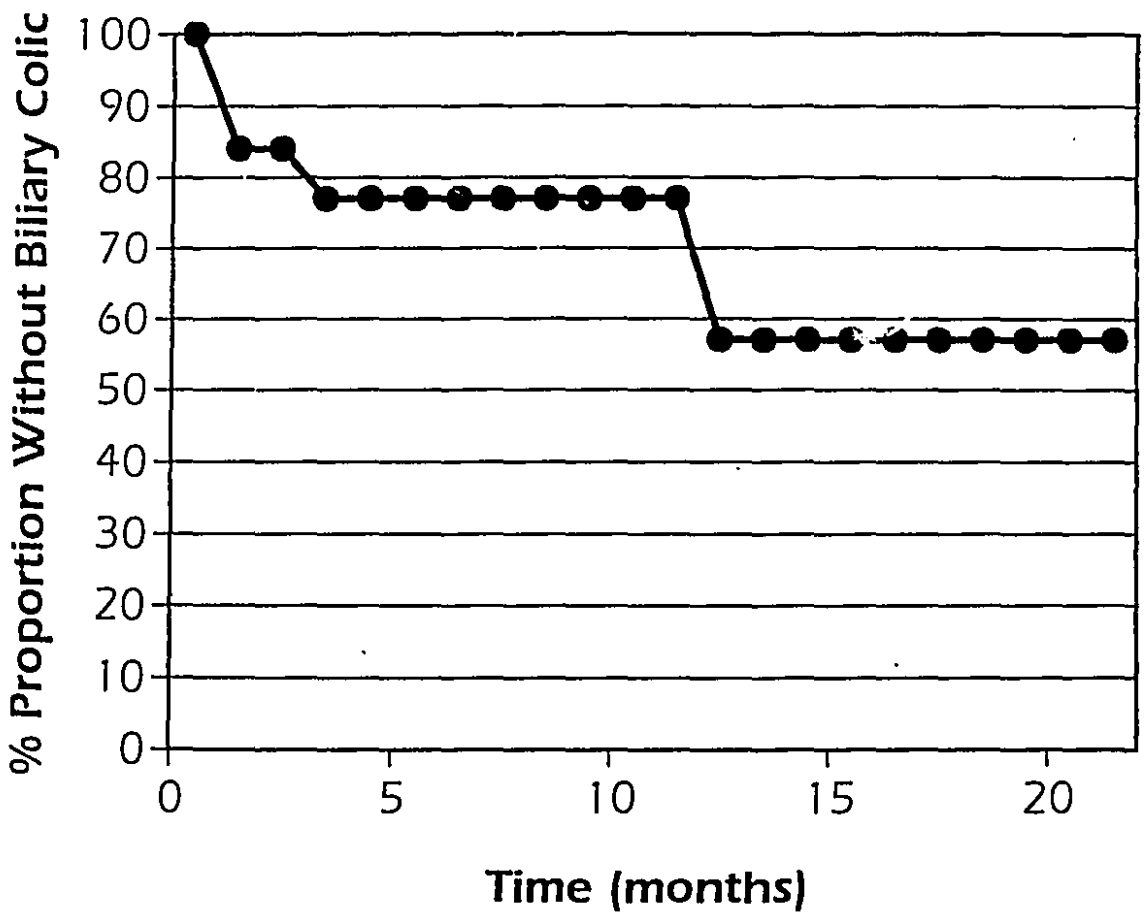

% Proportion Convalescing
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
Time (days)

Figure 3: Life table analysis of recurrent biliary colic following ESWL.


% Proportion Without Biliary Colic
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
Time (months)

biliary colic or personal choices resulted in the wish of 9 (28%) ESWL patients to cross-over to LC. At a telephone follow-up interview three years following ESWL treatment, only 4 (12%) had actually undergone LC. All follow-up results are detailed in table 3.

In addition to one LC patient having experienced recurrent colic 15 months following surgery, another LC patient developed a postoperative incisional seroma requiring 5 extra clinic visits in follow-up. Five (16%) ESWL patients terminated ursodeoxycholic acid treatment, including three due to presumed side effects (rash, nausea and diarrhea). Two (6.1%) ESWL patients developed biliary colic in the post-lithotripsy follow-up requiring hospital admission, one of whom required ERCP and bile duct stone removal after endoscopic sphincterotomy. This patient had crossed over to LC and had been operated on three months earlier. Another (3%) ESWL patient required an ERCP due to pancreatitis following lithotripsy with endoscopic sphincterotomy and fragment removal. One (3%) ESWL patient died during follow-up of a myocardial infarction. He had shown complete stone disappearance 3 months following lithotripsy.

The total disability duration was 6.8 ± 8.5 days for the ESWL, and 22.7 ± 16.6 days for LC patients at a median of 15 and 18 months follow-up respectively ($P < 0.01$). The detailed components constituting the durations of disability for each treatment group are shown in (table 4).

For both the ESWL and LC groups, significant improvements in quality of life assessments occurred one month following treatment when compared to pre-treatment

Table 3: Results of follow-up (up to 24 months)

	ESWL (N=32)	LC (N=25)
median (range) of follow-up	15 (1-24) mos	18 (1-21) mos
Patients with		
biliary colic	22 (68%)	1 (4%)
significant biliary colic	6 (18%)	1 (4%)
Mean time to significant biliary colic	3.4±3.6 mos	15 mos
Time away from usual activities due to post-treatment colic	7.6±15 days	6 days
Cross-overs (ESWL to LC)	9 (28%) (4 already operated)	------
Ursodeoxycholate side-effects	5 (16%)	------
Stone recurrence	1 (3%) 18 mos post-disappearance	------
Duration of convalescence	0.5±1.2 days	18.2±16.8 days
Total disability duration	6.8±8.5 days	22.7±16.6 days

Significant biliary colic is defined as a recurrent episode of pre-operative pain requiring time away from usual daily activities.

Total disability duration is a sum variable which includes all time away from usual daily activities due to gallstone disease symptoms and or complications, initial or follow-up visits and post-treatment convalescence using the intention-to-treat principle.

Table 4: Details of the different components used to tabulate the days of disability attributable to each treatment.

	ESWL (N=32)	LC (N=25)
Pre-treatment evaluation*	1±0 day	0.5± day
Duration of hospitalization	------	2.76±1.53 days
Time off for out-patient session	0.79±0.48 days	------
Convalescence	0.51±1.23 days	18.2±16.8 days
Follow-up related time-off (median 15 months for ESWL, 18 months for LC)	2.02±0.98 days (includes 1 patient with recurrent colic)	1.04±0.2 days
Recurrent biliary colic for ESWL	7.56±14.6 days (amongst the n=22 patients with recurrent colic)	------
Duration of disability	6.83±8.5 days	22.7±16.6 days

*Arbitrary choice of duration

values ($P<0.01$). Significant amelioration in VAS, NHPQ, and GGQLQS were noted at each follow-up visit up to six months for LC. These were slower to improve, yet continued to do so till 12 months for ESWL patients. Between group differences were not significant, yet the inter-group differences in incremental improvements of quality of life assessments were significantly greater for the LC group at 6 and 12 months ($P<0.01$). These results are shown in figure 4.

Cost analysis

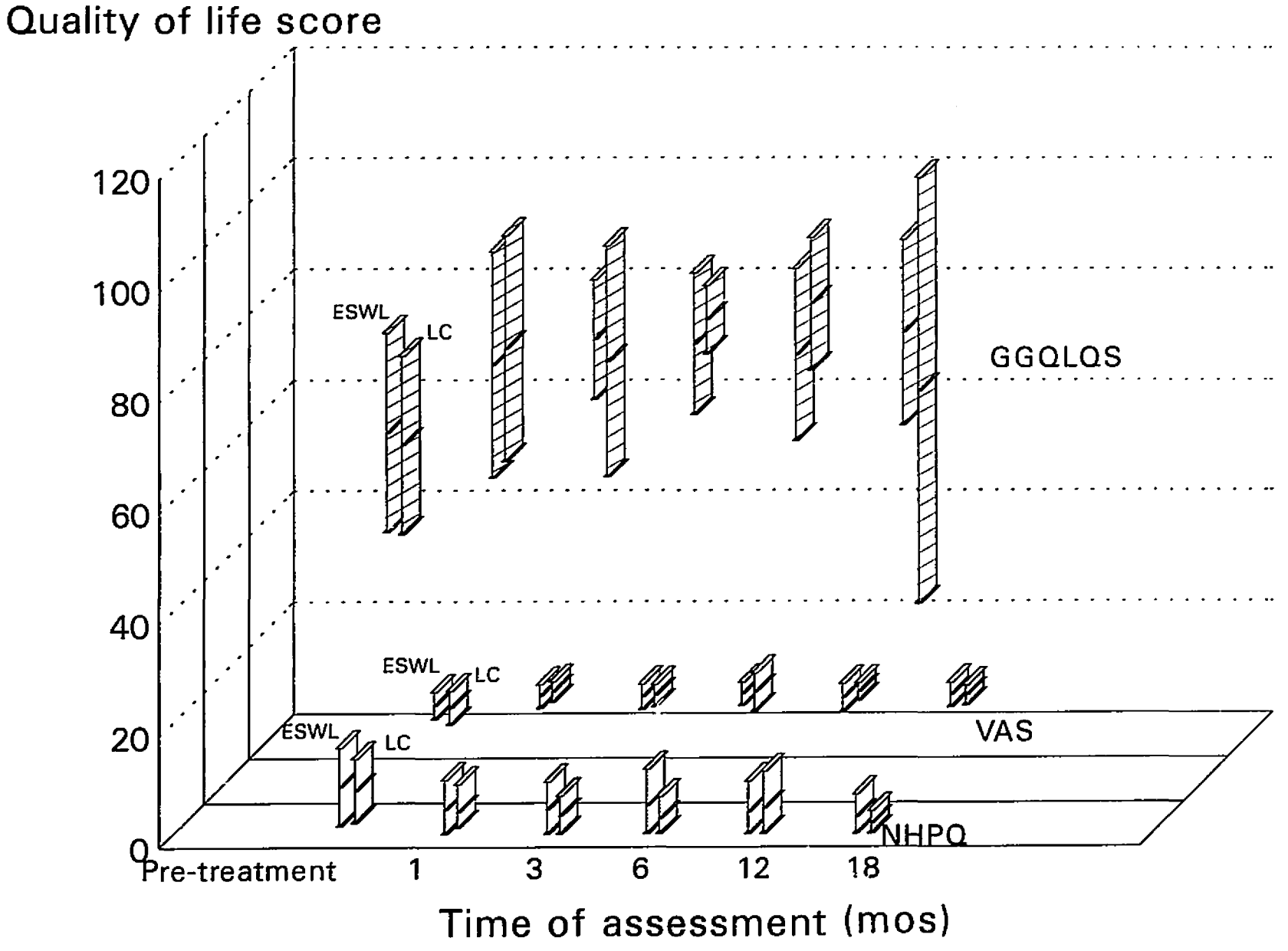
The crude accounting of costs related to ESWL and LC have previously been reported in an analysis prepared for the Conseil d'Évaluation des Technologies de la Santé du Québec (200). A set of tables detailing the cumulative costs reported below can be found in appendix.

The lithotripter in use at the study sites cost $1.6 million in 1990. This equipment was being used in 750 patients suffering from cholelithiasis and, mostly, nephrolithiasis per year. The special arm cost $400 thousand and is used by all cholelithiasis patients and 33% of those with urolithiasis. Based on 1990 levels of use and typical amortization rates, the unit cost associated with 7 years amortization and 50 biliary patients per year, $806, was taken as the best estimate, and the two extremes, $630 and $1,040, as the lower and upper bounds. The laparoscopic cameras and accessories cost $44,906 and the laparoscopic sets $22,056 if non-disposable trocars were included, and $20,357 if they were not. Disposable trocars cost $344 per use. Using the same criteria, $361 was selected as the best estimate, $260 as the

Figure 4: Results of quality of life assessments in both groups following treatment.

The Nottingham Health Profile Questionnaire decreases with improving health status whereas the German Gastrointestinal Quality of Life Questionnaire Score and the Visual Analogue Score increase with improving health status.

For both the ESWL and LC groups, significant improvements in quality of life assessments occurred one month following treatment when compared to pre-treatment values ($P<0.01$). Significant amelioration in VAS, NHPQ, and GGQLQS were noted at each follow-up visit up to six months for LC. These were slower to improve, yet continued to do so till 12 months for ESWL patients. Between group differences were not significant, yet the intra-group differences in incremental improvements of quality of life assessments were significantly greater for the LC group at 6 and 12 months ($P<0.01$).


Quality of life score
120
100
80
60
40
20
0
ESWL
LC
GGQLQS
ESWL
LC
VAS
ESWL
LC
NHPQ
Pre-treatment
1
3
6
12
18
Time of assessment (mos)

lower bound and $701 as the upper bound.

On average among patients evaluated for LC (this includes 37 additional patients randomized to the study previously reported comparing LC to mini-cholecystectomy [9]), the cost of pre-treatment evaluation was $406 (range: $255 - $854), and among the patients evaluated for lithotripsy, $341 (range: $273 - $605). The costs of the items specified by the protocols for each intervention were $272 for LC, and $240 for lithotripsy. As these exceed the lower bounds of the respective costs estimated from the charts, it appears that for some patients part of the evaluation was realized in the referring institution and was not repeated in the study institutions. Thus, for this analysis, the protocol costs were taken as the lower bound.

The average intervention cost for LC was $2,450 (range: $1,588 - $4,200). For lithotripsy, costs were estimated separately for each session (1st, 2nd, 3rd) and they covered the resources consumed in hospital for the session and any ultrasounds done within 10 days after the session. Any resources used between sessions but more than 10 days from the preceding session were considered in follow-up costs. On average, the first lithotripsy session cost $537 for physician fees, hospital services, imaging, procedures, tests and medications other than ursodeoxycholic acid. The second session cost, on average, $522; and the third session $519. To these costs must be added the average $818 cost per session of the specialized equipment, bringing the average cost per session to $1,344. Half of the patients undergoing lithotripsy and not converting to other modalities had only one session, 36% had three, while the remaining 14% had two sessions. Using these proportions, the

weighted average cost per patient undergoing lithotripsy was $2,496. To this cost must still be added the cost of ursodeoxycholic acid. On average, patients undergoing lithotripsy consumed 630 tablets of ursodeoxycholic acid for an added cost of $756. This average may be misleading because the proportions of 1, 2 and 3 sessions observed in the study may not reflect stable long term proportions. Nevertheless, no better estimates were available. Thus, the average total intervention cost per patient undergoing lithotripsy was estimated to be $3,252 (range: $561 - $4,188).

Uncomplicated follow-up costs through month 18 were $32 for laparoscopic and $284 for lithotripsy. To these uncomplicated follow-up costs would need to be added the proportional costs of managing complications. However, there were very few complications in the study and the sample size was to small to permit estimation of the relevant proportions with any degree of precision.

The use of laparoscopic cholecystectomy for the management of symptomatic gallstones cost, on average, $2,889 for evaluation, intervention and follow-up. The least expensive course of treatment came to $1,609, and the most expensive to $3,775. If all the upper bounds are summed, the highest cost came to $5,086 and adding the lower bounds gave a lowest cost of $1,863. These estimates of overall costs of laparoscopic surgery did not include the costs of managing complications. Weighted addition of costs related to conversion to open cholecystectomy assumed to be 2.7% (9) (the cost of which has been calculated previously [200]) would bring the total cost for LC to $2,906. One additional factor to consider is variation in the cost of the specialized laparoscopic equipment. If only disposable trocars were used, the

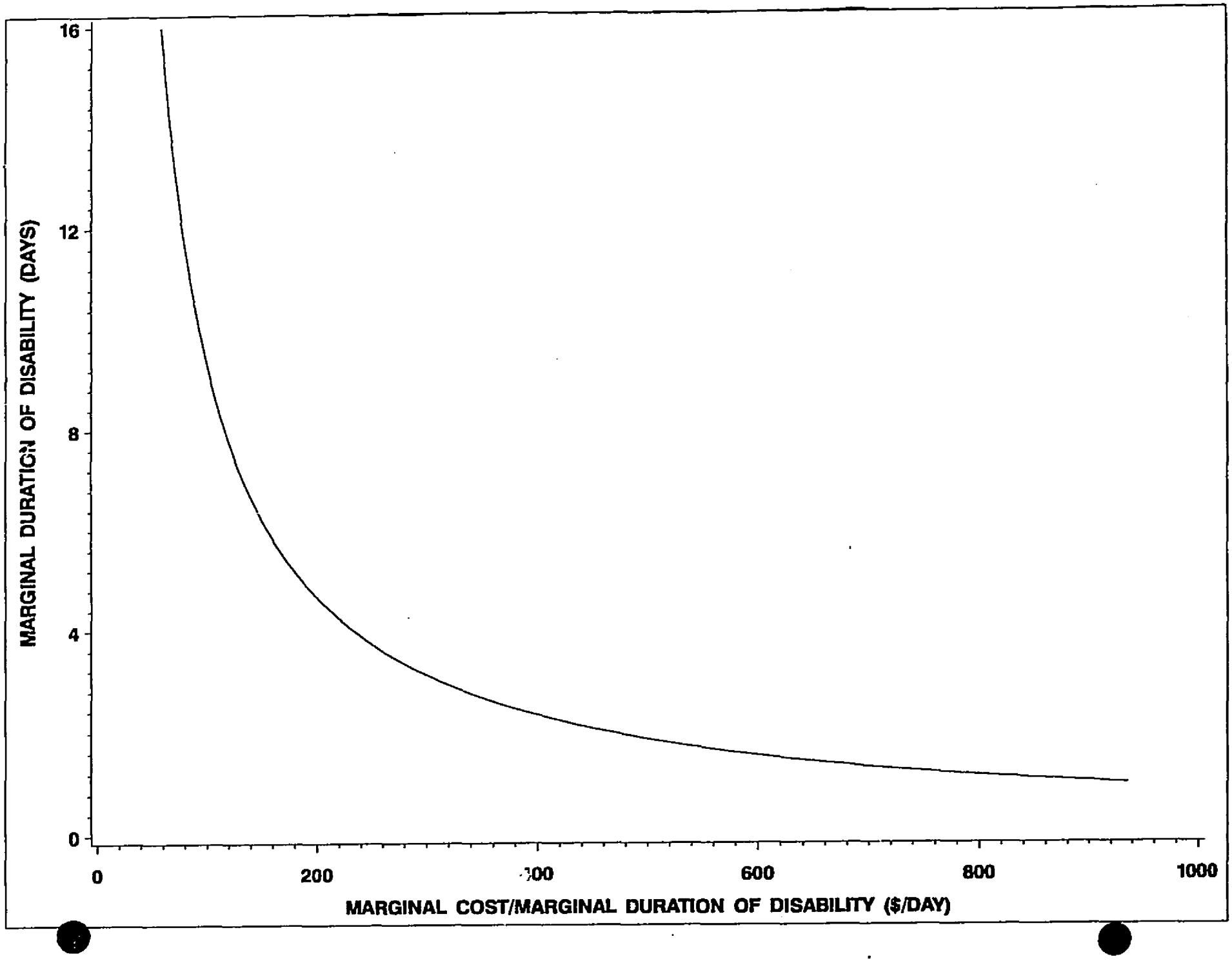
overall cost rose to $3,076, and if, in addition, the equipment was amortized over 5 years instead of 7, the overall cost would be $3,150.

On average, the cost of evaluation, intervention, follow-up and ursodeoxycholic acid for patients managed with lithotripsy came to $3,825. The least expensive patient cost only $1,096 and the most expensive $4,435. The sum of the lower bounds came to $1,047 and of the upper bounds to $5,006. Although as with the other two interventions, the complications of lithotripsy were not included. Even if the costs of the specialized equipment were amortized over 10 years and the equipment was used for 100 biliary lithotripsy sessions per year, the overall cost would drop to only $3,637, still far above the costs of LC.

Determination of cost-effectiveness

Using the incremental increase in cost for ESWL as compared to LC discussed above as numerator ($3825-2889), and the marginal decrease in duration of disability as denominator (23-6.8 days), ESWL resulted in an extra cost of $58/extra day of disability saved over the first 15 months follow-up when compared to LC. A sensitivity analysis suggested that the ratio is quite sensitive to the durations of disability. For example, halving the duration of convalescence of LC patients would result in this marginal cost-effectiveness ratio rising to $293/day of disability saved (figure 5). Alternatively, if ESWL convalescence doubled (such as with further attacks of biliary colic in time), the ratio would rise to $108/day of disability saved (figure 5). The marginal cost-effectiveness ratios were less sensitive to actual total

Figure 5: Cost-effectiveness ratio for a fixed incremental cost as a function of a varying difference in duration of disability between LC and ESWL.

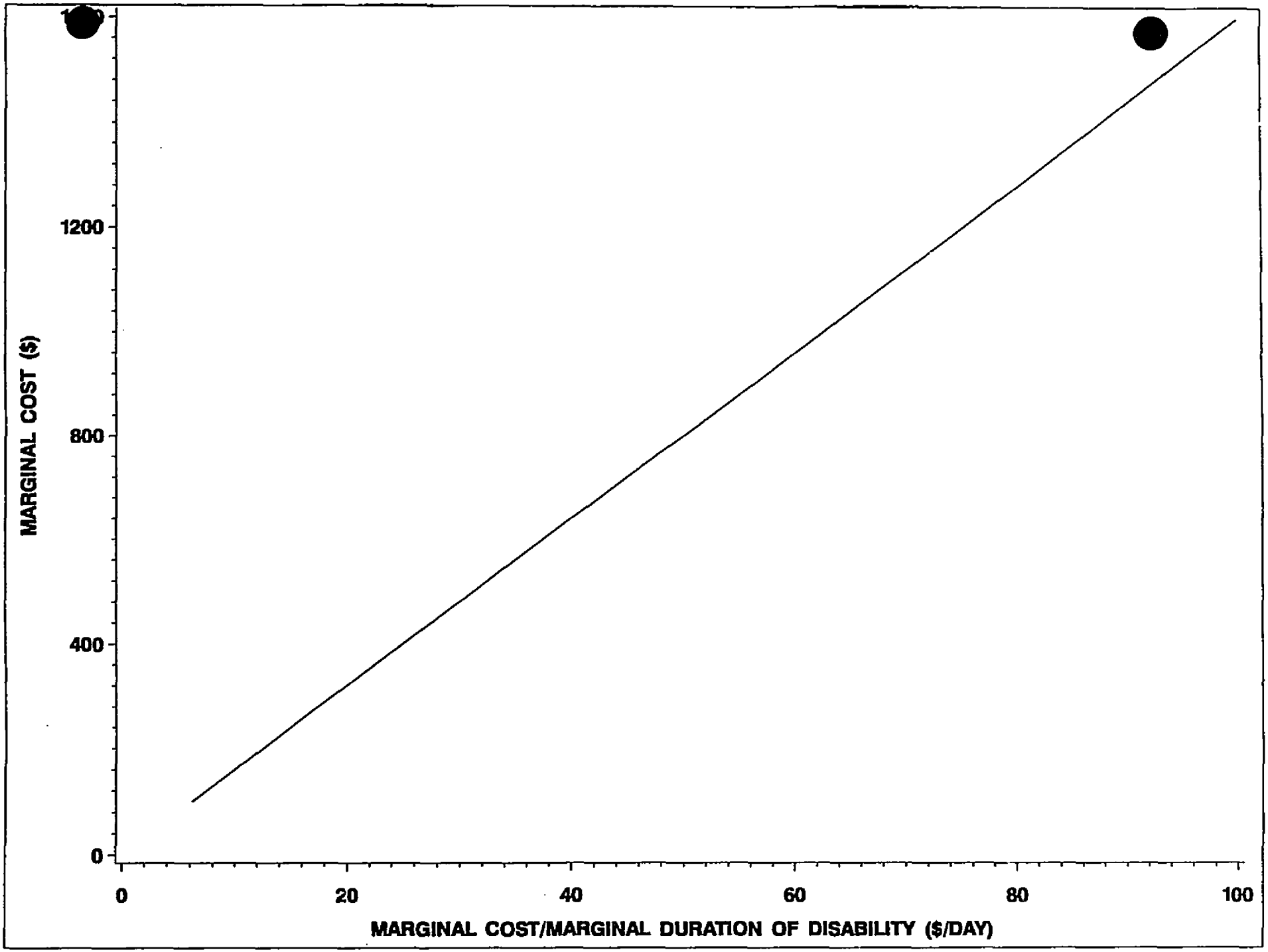

16
12
8
4
0
MARGINAL DURATION OF DISABILITY (DAYS)
0
200
600
800
1000
MARGINAL COST/MARGINAL DURATION OF DISABILITY ($/DAY)

costs. For example, using the highest cost estimate for ESWL and lowest cost estimate for LC would result in a ratio of $174.4/day of disability saved (figure 6).

DISCUSSION

This study is one of only three randomized controlled trials comparing a medical to a surgical treatment of symptomatic cholelithiasis (153,154), a condition which affects up to 3% of the North American population at a cost of nearly $5 billion dollars to the American Health Care System (1,10). It is the only study comparing the new gold standard treatment of LC (9,16) to ESWL. The paucity of formal evaluative trials in this important clinical area is attributable to the rapid emergence of ESWL in the mid-late 1980's followed by its supplantation by LC in the 1990's. Indeed, patient and physician pressures alike have dictated individual choices of treatment (8,87), and superseded any attempts at scientific characterization of effectiveness or cost considerations beyond data generated from case series of selected patients (119-150). Although most investigators agree that ESWL is of limited applicability (5), its reported effectiveness has varied widely because of many factors including patient selection, lithotripter generator type, adopted treatment protocols, and length of follow-up (5,149). The present trial was designed to determine the short-term efficacy, effectiveness and cost of ESWL as compared to LC, and provide descriptive data which could be used to counsel patients with symptomatic cholelithiasis when deciding on treatment, as is done for other diseases where both

Figure 6: Cost-effectiveness ratio for a fixed difference in duration of disability as a function of a varying marginal cost between LC and ESWL.


MARGINAL COST ($)
1200
800
400
0
0
20
40
60
80
100
MARGINAL COST/MARGINAL DURATION OF DISABILITY ($/DAY)

medical and surgical management are available such as benign prostatic hyperplasia (201,202).

Patient selection in the present study was very stringent compared to other groups (129-134) and was optimized to achieve the best possible results with a generator and a lithotripsy treatment protocol having yielded good stone fragmentation and disappearance rates in the past (138). Although stone fragmentation was deemed satisfactory in 78% of cases, the stone disappearance rate was modest reaching only 38% after 15 months. These results are in keeping with more recent reports in the literature (142,148,153,154), yet the reasons for the less than anticipated stone disappearance rates for the observed adequate fragmentation remain unclear. Possibilities include an inaccurate post-lithotripsy ultrasonographic assessment of fragmentation, and non compliance with the UDCA. The duration of convalescence for LC patients was more prolonged than in reports from uncontrolled LC series (6,7,14,15), yet is strikingly similar to results noted in LC groups from two previous randomized trials from separate continents comparing LC to open surgery (9,16). These reproducible discrepancies between controlled and uncontrolled trials emphasize the need for third party assessment of clearly defined outcomes (9), and perhaps identify some bias in the type of patient willing to enter such trials. Indeed, patient generalizability is a limitation of any randomized trial (8). Although only 16% of patients in the present study were excluded because of refusal of entry in the trial, others who did not meet inclusion criteria for stone number or size may have also refused to partake. A valid denominator is also very difficult to determine due to

varying referral practises. In addition, although the general demographics of excluded patients did not differ clinically from the study population, preliminary data (Barkun JS, personal communication) suggest that subtle baseline population characteristics which are difficult to quantify, such as patient expectation, may be significant determinants of post-operative convalescence. Other limitations of the present study include the small sample size which limited the power of certain inferences. As an example, stone burden on this study did not predict stone disappearance as a minority of ESWL patients had a large, or multiple stones. However, the principal goals of the study were not to examine predictors of fragmentation, dissolution, or determinants of post-operative convalescence, but rather to describe outcomes relevant to the patients (203). Major mortality and morbidity is unusual in symptomatic cholelithiasis. Indeed, Ransohoff et al., using decision modelling, concluded that some patients and physicians may decide that the risk of symptomatic gallstones is low enough that a policy of expectant management may be acceptable (55). Outcomes of interest must therefore focus on quality of life considerations including patients' symptoms and the impact they perceive these symptoms as having on their daily activities. This is why the present study examined symptom recurrence, quality of life and the composite index of duration of disability. The latter, with a determination of costs, formed the basis for the cost-effectiveness analysis. The best proof of the unpredictable nature of the interpretation of symptoms by patients is underscored by examining the fate of the 9 patients having expressed their intent to cross-over from ESWL to LC during the study. Only 4 of 9 (44%) had actually gone ahead with surgery within three years

following ESWL in a follow-up phone survey. Although no formal utility scoring was carried out, it is clear that the patients still refusing surgery were willing to tolerate possible recurrent colic for an unknown period of time rather than going through with surgery.

The study was not designed to address outcomes occurring in the longer term such as post-operative retained stones, and post-ESWL stone recurrence. It is interesting to note, however, that 5/6(83%) ESWL patients experiencing recurrence of symptoms of significant biliary colic had done so within the first month following ESWL. Moreover, this proportion of patients was significantly greater than that of patients experiencing milder colic recurrence over the initial 4 weeks following treatment. This suggests that, with up to 15 months median follow-up, most patients who will experience significant biliary colic will do so early on following ESWL. These data may be supported by previous observations suggesting that the yearly risk of biliary colic decreases with the passage of time inboth symptomatic and asymptomatic gallstone bearers (46,53). Predictors of who will and who will not experience colic recurrence however remain unknown.

Nicholl et al. in a previous randomized trial comparing ESWL to open surgery had noted a substantial reduction in the mean number of episodes of biliary pain per week during the twelve months following treatment (153). These investigators noticed, as with the present study, a dissociation between improvement in quality of life (health gain) and stone disappearance. In the only other randomized trial comparing ESWL to open cholecystectomy published by Plaisier et al., quality of life

measurements improved at 3 and 6 months following ESWL despite a stone disappearance rate of only 48% at 18 months (154). In the present study, the improvements in quality of life indices followed the course of biliary colic symptoms, even in the absence of stone disappearance. There was an immediate significant post-treatment improvement in the quality of life in both groups, followed by a rapid continued bettering in the LC group but not as marked in the ESWL group at 6 and 12 months. The role of UDCA in alleviating symptoms remains unclear (105-107,112-113). These findings further support the choice of patient relevant endpoints such as quality of life and duration of disability as the main outcomes of interest; they also validate the emphasis placed on more comparable outcomes between medical and surgical treatments of symptomatic cholelithiasis. Although the symptoms of typical biliary colic may be difficult to clearly delineate (36), so-called non specific symptoms are no more common in a population of gallstone bearers than in a population of patient without gallstones (28,33,34,35). In addition, as symptoms recur in 50-75% of patients treated for such complaints (70,170), the present study did not examine changes in such symptoms in contrast to other studies (153,154).

The cost data were prospectively gathered amongst each randomized group of patients according to the intention-to-treat principle and reflected the actual expenditures. The overall costs tabulated may be overestimates with regards to the costs attributable to equipment and personnel as some overlap may exist between both treatment alternatives. This analysis did not factor in indirect costs because of the difficulty in their determination (179). Had these been factored in, they might have

favoured ESWL (10). The cost of clinically significant complications, which occur with a low frequency for each treatment (5,14,65) were not included directly. Their possible impact can be extrapolated from the cost ranges examined in the sensitivity analysis. The life-time horizon adopted was limited and does not take into consideration stone recurrence following stone disappearance. Follow-up studies suggest that stone recurrence approximates $31 \pm 7\%$ with symptomatic recurrence in 61% over the next 5 years (162).

The cost-effectiveness ratios obtained are particularly sensitive to the marginal difference in durations of disability (figure 5), and vary less with incremental costs (figure 6). ESWL would appear most cost-effective in patients who can be expected to have a prolonged convalescence following LC such as those in whom conversion to open surgery may be more likely (204). With increasing frequencies of significant biliary colic following fragmentation, ESWL becomes, of course less cost-effective. Yet there is no information as to long-term significant biliary colic recurrence rates.

Many studies have examined the cost-effectiveness of treatments of gallstone disease (172-181), but few have contrasted ESWL to LC, or satisfy criteria assessing the adequacy of the analysis (171). Nicholl et al. showed in their randomized controlled trial that ESWL was "at least as cost-effective" as open cholecystectomy for patients with a small gallstone burden (153). A thorough decision analysis performed by Bass et al. suggested that the resulting marginal cost-effectiveness of ESWL vs. open cholecystectomy is $216,000 of extra charges per year of life gained with ESWL (179). Adjusting for effects of morbidity on quality of life, ESWL was

projected to have slightly better quality-adjusted survival than open cholecystectomy for the small subset of patients with one stone (by 8 to 43 days at 5 years) but not for young patients with multiple stones. However, this analysis focused primarily on direct, not indirect costs and on mortality and significant morbidity, not quality of life considerations due to a paucity of data on this key aspect when examining the impact of gallstone disease (10).

Two more recent analyses examined open cholecystectomy, LC, and ESWL (180-181). The two studies arrived at opposite conclusions with regards to the cost-utility of LC versus ESWL. These studies highlighted the absence of meaningful data adapted to an acute intermittent illness followed by full health, and the consideration or exclusion of indirect costs along with the perspective adopted for the analysis (individual versus societal).

The present study provides some questions and answers to these important questions. Perhaps only a subgroup of patients with symptomatic gallbladder stone disease should be offered any treatment. Nonetheless, what seems clear is that gallbladder stone ESWL is of limited applicability with the available generator technologies. Furthermore, the effectiveness of ESWL is only modest in achieving stone disappearance, and most certainly at present, a majority of patients with symptomatic cholelithiasis will opt for LC, particularly young patients because of the risk of stone recurrence. Yet in the absence of stone disappearance, ie: despite the persistence of fragments, time away from daily activities is minimal, presumably mostly owing to the natural course of symptomatic gallstone disease, although an

effect attributable to ESWL and UDCA cannot be ruled out. Controlled trials assessing the role of UDCA or ESWL on symptoms, observational studies examining predictors of significant biliary colic recurrence following ESWL, and further follow-up are now required to assess the validity of these conclusions.

CONCLUSION AND SUMMARY

Based on our findings, and the existing data in the literature at this time, we recommend that patients who are candidates for ESWL be appraised of its existence as a therapeutic modality. Patients who would like to avoid, or who are not candidates for surgery should be offered ESWL, as should patients expected to have a prolonged convalescence following LC. Other patients should decide on a treatment option based on their subjective quality of life interpretation of available objective data on symptom recurrence and duration of disability attributable to each technique.

ACKNOWLEDGEMENTS

I would like to acknowledge the following colleagues and family for assistance provided in the collection, analysis, interpretation and preparation of the original data presented in this thesis.

Dr. Jeffrey Barkun for assistance, support, and stimulation during all phases of research work.

Dr. R. Battista, Dr. C. Goresky, Dr. J. Bailar, Dr. L. Joseph for assistance in study design.

Ms C. Wickham, Ms D. Thibault for assistance in data collection.

Drs. G. Fried, J Meakins, J. Hinchey, A. Hreno, D. Owen, H. Sigman, P. Bret, R. Brassard, L. Stein, P. Szego, P. Cleland, D. Daly, C. Goresky, and other members of the McGill Gallstone Treatment Group for assistance in patient accrual and treatment.

Dr. J. Sampalis, and Dr. L. Joseph for assistance in data entry and analysis.

Ms. E. Trindade, Dr. J. Caro, and Dr. M. MacGregor for assistance in the collection, analysis, and interpretation of the rough cost data.

Dr. C. Goresky whose continued guidance and support allowed me to bring this research forward and to its completion.

Dr. P. Cotton who was and will always be my mentor and friend.

Dr. S. Grover for constant support and guidance as thesis supervisor.

The thesis reviewers for taking the time to evaluate this work.

This work was funded by a clinical trial research award from the Fonds de la Recherche en Santé du Québec. The cost data was collected in part with the support of the Conseil d'évaluation des technologies de la santé du Québec.

Dr. A Barkun received personal support as an FRSQ Fellow, and later as a Chercheur Clinicien Boursier Junior I.

I would also like to acknowledge my parents for providing me with the moral and work ethics which have allowed me to carry out my research.
I also acknowledge the unconditional and continued support and guidance of my wife Hillary without whom this project would not have come to completion.

Lastly, I dedicate this thesis to the memory of A. Wiese-Hansen.

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APPENDICES

The mortality attributable to cholelithiasis in Canada

See tables 1-8

NUMBER OF DEATHS BY AGE FOR EACH OF THE 8 YEARS 1950, 55, 60...85:
(/000)

Age	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	Tot
1950										
M	0	0	1	3	15	29	38	53	27	166
F	0	0	4	22	27	58	92	73	50	326
1955										
M	0	0	1	6	8	21	46	71	26	179
F	0	1	1	9	28	35	90	99	56	319
1960										
M	0	0	0	4	11	26	37	75	55	208
F	0	1	4	13	16	33	69	99	67	302
1965										
M	0	0	1	3	6	18	42	74	67	211
F	0	1	4	13	18	31	65	103	107	342
1970										
M	0	0	2	4	14	19	21	51	48	159
F	0	0	4	4	12	23	36	75	75	229
1975										
M	0	0	0	0	3	7	16	30	35	91
F	0	0	2	0	3	8	16	31	62	122
1980										
M	0	0	0	2	0	6	13	37	28	86
F	0	0	0	0	2	6	15	23	63	109
1985										
M	0	0	1	1	2	6	9	28	37	84
F	0	0	1	1	1	3	11	28	58	103

ICD DISEASE CLASSIFICATION MODIFICATIONS OVER TIME:

***For 1950-55-60**

A-106=cholecystitis and cholelithiasis
(probable overestimation of disesee specific deaths for gallstone disease)

***For 1965**

584=cholelithiasis
585=cholecystitis and cholangitis without mention of calculi
586=other diseases of gallbladder and bile ducts
I used 584+585 (probable overestimation of disease specific deaths for gallstone disease)

***For 1970**

574=CHOLELITHIASIS
- .0=gallbladder with acute cholecystitis
- .1=gallbladder with other cholecystitis
- .2=gallbladder without mention of cholecystitis
- .3=bile duct with acute cholecystitis
- .4=bile duct with other cholecystitis
- .5=bile duct without mention of cholecystitis
- .9=other and unspecified

575=OTHER DISEASES OF GALLBLADDER
I used 574 only (closer to correct diagnostic category, slight overestimation probable for disease specific deaths for gallstone disease)

***For 1975**

574=unchanged
575=CHOLECYSTITIS WITHOUT CALCULUS
576=OTHER DISEASES OF GALLBLADDER
- .0=obstruction
- .1=fistula
- .9=other and not specified

I used 574 only (some of 576 should belong to 574- unable to say which so some underestimation of gallstone related deaths)

***As of 1980**

574=unchanged
575=OTHER DISEASES OF GALLBLADDER
- .0=acute cholecystitis
- .1=other cholecystitis
- .2=obstruction
- .3=hydrops
- .4=perforation
- .5=fistula
- .6=cholesterolosis
- .8=other
- .9=not otherwise specified

576=OTHER DISEASES OF BILIARY TREE
- .1=cholangitis
- .2=obstruction of bile duct
- .3=perforation of bile duct
- .4=fistula
- .8=other
- .9=not specified(No expected change of events distribution on the basis of this change in disease classification- at least in regards to gallstone disease)

AGE SPECIFIC DEATH RATES FOR CHOLELITHIASIS IN CANADIAN WOMEN FOR EACH OF THE 8 YEARS 1950, 55, 60...85:

Figures are rates/1000

Age	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
1950 F*	0	0	0.004	0.021	0.035	0.097	0.21	0.22	-
1955 F*	0	0.0007	0.0009	0.008	0.03	0.008	0.19	0.33	0.57
1960 F	0	0.0007	0.003	0.01	0.015	0.044	0.13	0.29	0.60
1965 F	0	0.0005	0.01	0.01	0.024	0.036	0.11	0.27	0.73
1970 F	0	0	0.002	0.003	0.009	0.023	0.053	0.17	0.41
1975 F	0	0	0.001	0	0.002	0.07	0.02	0.06	0.22
1980 F	0	0	0	0	0.002	0.005	0.02	0.03	0.22
1985 F	0	0	0.0004	0.0004	0.0007	0.002	0.01	0.04	0.17

*For 1950, the denominator is that of the population in 1951
*For 1955, the denominator is that of the population in 1956

For 1950, the years 70-79 and 80+ are collapsed together in this table.

AGE SPECIFIC ADJUSTED DEATH RATES FOR CHOLELITHIASIS IN CANADIAN WOMEN AGED 50 AND OVER FOR EACH OF THE 8 YEARS 1950, 55, 60...85:

Standard year taken is 1985.
Total population of females age 50 and over in 1985: (/000)=3353.7

Year	Direct standardization adjusted death rates	Indirect standardization adjusted death rates
1950	0.17	0.15
1955	0.192	.17
1960	0.18	.20
1965	0.18	.15
1970	0.10	.08
1975	0.07	.08
1980	0.03	.04

There is fluctuation over time which may reflect in part variablility of age (gallstone disease mortality is very age dependent), but also reflects changes in ICD-9 classification. I believe that it is important to standardize.

AGE SPECIFIC ADJUSTED DEATH RATES FOR CHOLELITHIASIS FOR ALL CANADIAN WOMEN FOR EACH OF THE 8 YEARS 1950, 55, 60...85:

Year	Direct standardization adjusted death rates		Indirect standardization adjusted death rates	
		CMF		SMR
1950	0.05	6.2	0.13	16
1955	0.06	7.5	0.07	8.6
1960	0.05	6.2	0.06	7.6
1965	0.05	6.2	0.06	7.0
1970	0.03	3.7	0.03	3.9
1975	0.02	2.5	0.01	1.7
1980	0.01	1.2	0.01	1.2

Note: SMR and CMF expressed as ratio, not as percentage.

KERRIDGE FORMULA INVERSE SMR'S FOR SELECTED AND ALL AGE GROUPS OF CANADIAN WOMEN FOR EACH OF THE 8 YEARS 1950, 55, 60...85:

Year	Inverse SMR's for all age groups	Inverse SMR's for Canadian women aged 50 and over
1950	21	29
1955	12	19
1960	10	15
1965	8.1	13
1970	5.1	7.6
1975	6.8	2.1
1980	6.8	1.7

Note: Inverse SMR expressed as ratio, not as percentage.

AGE SPECIFIC DEATH RATES FOR CHOLELITHIASIS IN CANADIAN WOMEN FOR EACH OF THE 8 YEARS 1950, 55, 60...85: - COHORT ANALYSIS -

Figures are rates/1000

Age	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
1950 F*	0	0	0.004	0.021	0.035	0.097	0.21	0.22	
1960 F	0	0.0007	0.003	0.01	0.015	0.044	0.13	0.29	0.60
1970 F	0	0	0.002	0.003	0.009	0.023	0.053	0.17	0.41
1980 F	0	0	0	0	0.002	0.005	0.02	0.03	0.22

*For 1950, the denominator is that of the population in 1951

For 1950, the years 70-79 and 80+ are collapsed together in this table.

The highlighted diagonal gives the ordinates (mortality rates) for varying abscissa (years) for the cohort of females born in 1950. Similar analysis are performed for cohorts (grouped in 10 year intervals) of females born between 1880 and 1950 (as there was no reported mortality as of 1980 for women born after 1950).
With this data, the corresponding cohort contours plotting alternately death rate and log (death rate) vs age are shown in the figures below.

PYLL FOR WOMEN AGED 50-59 AND 60-69 FOR THE YEARS 1950-1980 (USING A CUT-OFF AT AGE 70 AND 1985 AS STANDARD YEAR):

(Final age adjusted results are given only for PYLL to age 70)
(Total female population aged 50-69 in 1985: 2302400)
(Age adjusted rates of PYLL are expressed /000)

Age		50-59	60-69	Total	Rate of PYLL
Remaining years with cut-off at age	70	15.5	5.5		
	80	25.5	15.5		
For year 1950					
Number of deaths		58	92		
PYLL to age 70		899	506	1405	
Correcting factor		0.95	1.07		
Age-adjusted PYLL		854	541	1395	0.61
For year 1955					
Number of deaths		35	90		
PYLL to age 70		542.5	495	1037	
Correcting factor		0.93	1.10		
Age-adjusted PYLL		505	545	1050	0.46
For year 1960					
Number of deaths		33	69		
PYLL to age 70		511.5	379.5	891	
Correcting factor		0.92	1.12		
Age-adjusted PYLL		471	425	896	0.39
For year 1965					
Number of deaths		31	65		
PYLL to age 70		480.5	357.5	838	
Correcting factor		0.90	1.15		
Age-adjusted PYLL		432	411	844	0.37
For year 1970					
Number of deaths		23	36		
PYLL to age 70		356.5	198	555	
Correcting factor		0.92	1.12		
Age-adjusted PYLL		328	222	550	0.24
For year 1975					
Number of deaths		8	16		
PYLL to age 70		124	88	212	
Correcting factor		0.98	1.20		
Age-adjusted PYLL		122	106	227	0.10
For year 1980					
Number of deaths		6	15		
PYLL to age 70		93	82.5	176	
Correcting factor		0.95	1.07		
Age-adjusted PYLL		88	88	176	0.08
For year 1985					
Number of deaths		3	11		
PYLL to age 70		46.5	60.5	107	
Correcting factor		1	1		
Age-adjusted PYLL		47	61	108	0.05

A COMPARISON OF AGE ADJUSTED PYLL (to age 70) TO AGE SPECIFIC ADJUSTED DEATH RATES TAKING 1985 AS REFERENCE OR STANDARD YEAR:

Year	Direct standardization adjusted death rates	PYLL to age 70 after age adjustment (1985=ref yr)
1950	0.05	0.61
1955	0.06	0.46
1960	0.05	0.39
1965	0.05	0.37
1970	0.03	0.24
1975	0.02	0.10
1980	0.01	0.08
1985	0.01	0.05

The age standardized death rates were calculated including the population of women ages 70 and above. Although the overall trend is downward in both, the drop in the early years is much more marked for the age adjusted PYLL. Thereafter, both plateau off, and this flattening is much more dramatic in comparison to the initial values in the age adjusted PYLL. I believe that the discrepancy in "amplitude of the trend" is artificial and due to the fact that for the PYLL, we have excluded the population over 70 years of age: a population where the mortality is much higher for cholelithiasis. In fact, if we would do a "PYLL with a cut-off at age 80 or 85, I believe the numbers would be more comparable for both measures as the excess mortality is much higher (even though the amount of "added years of life" is smaller). This contrasts with what is usually expected from PYLL where the population outweighs the added years of life considerations numerically; but we are in the case of cholelithiasis where the mortality is very low, and much more marked in the very old age groups. A quick look at the table displaying the number of deaths shows this well.

Treatment protocol for laparoscopic cholecystectomy (9)

Anaesthesia: general

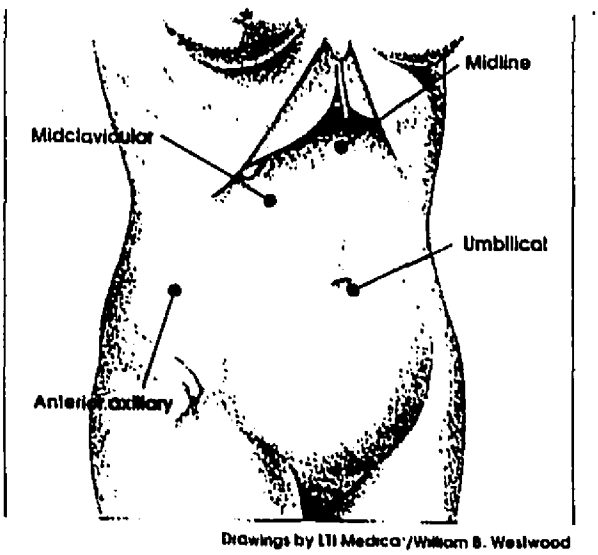
Position: supine, legs in stirrups, thighs horizontal, knees flexed 90 degrees.

Preoperative: Foley catheter, nasogastric tube, monitoring of endtidal CO2 by anaesthetist. Procedure: (if no prior upper abdominal surgery)

Supra-umbilical 1.5 cm incision then insertion of Verys needle through umbilicus. Confirmation that needle is into free peritoneal cavity by saline drop test. Insufflation of peritoneal cavity with CO2 at 1-2 L/min ensuring that initial pressure is < 10 mmHg and maximal inflation pressure is $<$ 15-18 mmHg, depending on body habitus. Verys needle is then withdrawn and 10 mm disposable Ethicon trocar-cannula is placed into peritoneal cavity. CO2 line is attached to this cannula and CO2 insufflator set to maintain inflation pressure of 15-18 mmHg. The telescope is then inserted through the cannula, connected to the video camera and monitor, and the entire abdominal cavity is examined.

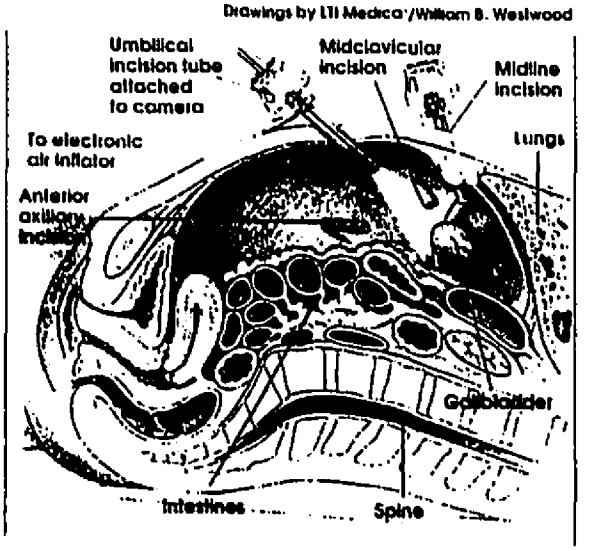
Three additional puncture sites are made for insertion of two 5 mm disposable Ethicon trocar-cannulas and one more 10 mm Ethicon trocar-cannula. Placement of these cannulas will be made according to the surgeon's preferences and the body habitus of the patient. The gallbladder will be grasped with a forceps and adhesions to it will be dissected using the hook dissector or dissecting forceps attached to electrocautery. The cystic artery and duct will next be identified, dissected, clipped with either absorbable PDS clips (medium-large, supplied by Ethicon), or metallic clips applied using the Ethicon clip applicator, and divided. The gallbladder will then be dissected from the liver bed using cautery. A cholangiogram

LAPAROSCOPIC CHOLECYSTECTOMY



Drawings by LTI Medical/William B. Westwood

INCISION SITES FOR LAPAROSCOPIC CHOLECYSTECTOMY



SIDE VIEW OF INSIDE OF ABDOMEN

will be performed at the discretion of the operating surgeon.

The gallbladder will then be grasped and removed via the umbilical port under direct vision placing the telescope through the other 10 mm port.

If indicated, the fascia of the umbilical puncture site will be closed using absorbable suture material supplied by Ethicon, and the skin incisions will also be closed using fine suture material supplied by Ethicon.

The Foley and nasogastric tubes will then be removed and the patient sent to the recovery room.

Treatment protocol for lithotripsy and bile acid dissolution

Two weeks prior to lithotripsy, the patient is started on oral bile acid therapy. Women of child-bearing age are asked to use a contraceptive method while they are on this regimen. Each patient is given a prescription for ursodeoxycholic acid to take (10 mg/kg/day) as a single nighttime dose. The patient remains on the oral bile acid until stone disappearance (proven by two ultrasound studies three months apart) or until the end of the study period, which will cover a total of 3 years for each patient. Should any patient develop significant diarrhea for which no cause can be found, or if a female patient wishes to become pregnant, the medication will be stopped, but scheduled lithotripsy will be carried out as for any other patient on this arm. The lithotripsy treatments are carried out on an out-patient basis with no analgesia, or minimal intravenous sedation if required in some patients (we anticipate that 50% of patients will require meperidine 50 mg, +/- diazepam 5-10 mg), after they have signed informed consent for the lithotripsy session. The sessions are carried out by

one of the co-investigators (Drs. Patrice Bret and Larry Stein) using the Lithostar+ machine, which is located at the Royal Victoria Hospital. This is an electromagnetic generator adapted for biliary use with the addition of an overhead arm which provides for ultrasonographic localization and targeting of the stones. Each patient will be treated in the left posterior oblique or prone position, depending on patient comfort and adequacy of stone targeting. The patient lies on the treatment table; there is no bath involved with this technology. The treatment will not be carried out if targeting cannot avoid the lung fields, abdominal and pulmonary cysts or angiomas. Ultrasonographic control of fragmentation will be carried out every 1000-2000 shocks, and frequent repositioning will be performed with the in-line probe as needed. Barring any complications during the procedure, lithotripsy is carried out until satisfactory fragmentation is achieved (only fragments 5 mm or less remain) or until a total of 4000 shock waves with a capacitor setting of 16-19 kV for a power level approximating 6 (138). Treatment will be stopped and rescheduled if at any time the operator feels that the patient may be at risk of developing cardiovascular instability or respiratory insufficiency. The patient will not be offered repeat treatments should such an eventuality occur in two successive attempts. Treatment will also be rescheduled if the patient experiences intolerable pain not responsive to the aforementioned doses of IV sedation, or should the patient strongly wish not to pursue the session . The total duration of the treatment is 45-60 minutes. Sessions are repeated bi-weekly up to a total of three sessions unless satisfactory fragmentation is achieved earlier. After the lithotripsy, an initial ultrasound check will be performed to assess fragmentation. After recovery, but prior to discharge from hospital, the patient

will fill out the McGill pain questionnaire and be given an appointment for repeat lithotripsy or follow-up by the nurse clinician.

The Nottingham Heath Profile Questionnaire

This version of the Nottingham quality-of-life index has been used in various clinical settings and presents many advantages, including its simplicity, sensitivity and broad coverage. Moreover, this has been the scale adopted in the Sheffield trial comparing cholelithotripsy to cholecystectomy, and preliminary data appear to confirm that using this scale, gallstone disease impairs health status appreciably. The NHP is based on answers to 38 questions grouped into six indices of subjective experience (194-198).

The McGill Pain Questionnaire

The MPQ has been widely used in clinical studies of several pain syndromes. It has been shown to have acceptable reliability even when applied retrospectively; its face validity has been demonstrated by the number and variety of studies in which it has been used. Construct validation studies have confirmed its theoretical framework in terms of its ability to distinguish the sensory, affective, and evaluative dimensions of pain. Criterion validity has been confirmed in terms of its concurrent, predictive and discriminative aspects. It takes an interviewer 15 to 20 minutes to administer it on a first occasion (189-193).

Note: EL = energy level, P = pain, ER = emotional reactions, S = sleep, SI = social isolation, PA = physical abilities

- Listed below are some problems people can have in their daily life.
- Please read each one carefully.
- If it is TRUE for you, put a tick (✓) in the box under Yes.
- If it is NOT TRUE, put a tick (✓) in the box under No.
- If you are not sure whether to answer yes or no to a problem, ask yourself whether it is true for you *in general.*

Note: it is important that you answer every question.

	Yes	No	Section
I'm tired all the time	☐	☐	EL
I have pain at night	☐	☐	P
Things are getting me down	☐	☐	ER
I have unbearable pain	☐	☐	P

	Yes	No	
I take tablets to help me sleep	☐	☐	S
I've forgotten what it's like to enjoy myself	☐	☐	ER
I'm feeling on edge	☐	☐	ER
I find it painful to change position	☐	☐	P
I feel lonely	☐	☐	SI

	Yes	No	
I can walk about only indoors	☐	☐	PA
I find it hard to bend	☐	☐	PA
Everything is an effort	☐	☐	EL
I'm waking up in the early hours of the morning	☐	☐	S

	Yes	No	
I'm unable to walk	☐	☐	PA
I'm finding it hard to make contact with people	☐	☐	SI
The days seem to drag	☐	☐	ER
I have trouble getting up and down stairs or steps	☐	☐	PA
I find it hard to reach for things	☐	☐	PA

	Yes	No	
I'm in pain when I walk	☐	☐	P
I lose my temper easily these days	☐	☐	ER
I feel there is nobody I am close to	☐	☐	SI
I lie awake for most of the night	☐	☐	S

	Yes	No	
I feel as if I'm losing control	☐	☐	ER
I'm in pain when I'm standing	☐	☐	P
I find it hard to dress myself	☐	☐	PA
I soon run out of energy	☐	☐	EL

	Yes	No	
I find it hard to stand for long (e.g. at the kitchen sink, waiting for a bus)	☐	☐	PA
I'm in constant pain	☐	☐	P
It takes me a long time to get to sleep	☐	☐	S
I feel I am a burden to people	☐	☐	SI
Worry is keeping me awake at night	☐	☐	ER
I feel that life is not worth living	☐	☐	ER

	Yes	No	
I sleep badly at night	☐	☐	S
I'm finding it hard to get on with people	☐	☐	SI
I need help to walk about outside (e.g. a walking aid or someone to support me)	☐	☐	PA

	Yes	No	
I'm in pain when going up and down stairs or steps	☐	☐	P
I wake up feeling depressed	☐	☐	ER
I'm in pain when I'm sitting	☐	☐	P

McGill - Melzack Pain Questionnaire

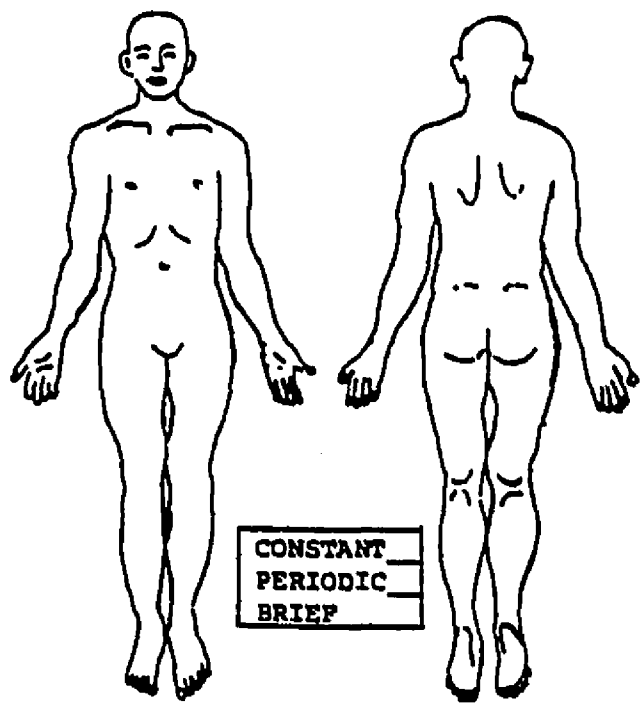
Patient's Name_____ Date_____ Time_____ am/pm
Analgesic(s) _____ Dosage_____ Time Given _____ am/pm
_____ Dosage_____ Time Given_____ am/pm

Analgesic Time Difference (hours): +4 +1 +2 +3

PRI: S_____ A_____ E_____ M(S)_____ M(AE)_____ M(T)_____ PRI(T)_____
(1-10) (11-15) (16) (17-19) (20) (17-20) (1-20)

1 FLICKERING	11 TIRING	
QUIVERING	EXHAUSTING	
PULSING	12 SICKENING	
THROBBING	SUFFOCATING	
BEATING	13 FEARFUL	
POUNDING	FRIGHTFUL	
2 JUMPING	TERRIFYING	
FLASHING	14 PUNISHING	
SHOOTING	GRUELLING	
3 PRICKING	CRUEL	
BORING	VICIOUS	
DRILLING	KILLING	
STABBING	15 WRETCHED	
LANCINATING	BLINDING	
4 SHARP	16 ANNOYING	
CUTTING	TROUBLESOME	
LACERATING	MISERABLE	
5 PINCHING	INTENSE	
PRESSING	UNBEARABLE	
GNAWING	17 SPREADING	
CRAMPING	RADIATING	
CRUSHING	PENETRATING	
6 TUGGING	PIERCING	
PULLING	18 TIGHT	
WRENCHING	NUMB	
7 HOT	DRAWING	
BURNING	SQUEEZING	
SCALDING	TEARING	
SEARING	19 COOL	
8 TINGLING	COLD	
ITCHY	FREEZING	
SMARTING	20 NAGGING	
STINGING	NAUSEATING	
9 DULL	AGONIZING	
SORE	DREADFUL	
HURTING	TORTURING	
ACHING	PPI	
HEAVY	0 No pain	
10 TENDER	1 MILD	
TAUT	2 DISCOMFORTING	
RASPING	3 DISTRESSING	
SPLITTING	4 HORRIBLE	
	5 EXCRUCIATING	

PPI_____ COMMENTS:



CONSTANT
PERIODIC
BRIEF

ACCOMPANYING SYMPTOMS:
NAUSEA
HEADACHE
DIZZINESS
DROWSINESS
CONSTIPATION
DIARRHEA
COMMENTS:

SLEEP:
GOOD
FITFUL
CAN'T SLEEP
COMMENTS:

ACTIVITY:
GOOD
SOME
LITTLE
NONE

FOOD INTAKE:
GOOD
SOME
LITTLE
NONE
COMMENTS:

COMMENTS:

Functional status index: The German Gastrointestinal Quality of Life Questionnaire Score (GGQLQS)

An international team of methodologists and surgeons developed a new system-specific index. In different phases, items were collected, tested, rejected or retained and finally verified by international experts. The instrument was also validated against other generic measures, it was compared to normals, tested for reproducibility with 50 stable patients and for responsiveness with 159 patients undergoing laparoscopic cholecystectomy. The product is a bilingual (German and English) questionnaire containing 36 items (199).

Consent form

I have been found to have gallstones which are thought to be the cause of my abdominal pain. Patients with abdominal pain caused by gallbladder stones are at risk for developing symptom recurrence over the next few years and may develop serious complications of gallstone disease such as pancreatitis (an inflammation of the pancreatic gland), cholecystitis (an inflammation of the gallbladder), or ascending cholangitis (an infection of the bile and bile ducts). Treatment of stones in the gallbladder is therefore indicated. The goal of this study is to determine whether certain patients will benefit from a modification of the standard treatment now available.

At present, surgical removal of the gallbladder, cholecystectomy, is the treatment of choice. However, over the last five years, a new non-surgical treatment has been used on over 7500 subjects in Europe, Asia, and more recently the United States. It

involves breakage of the stones with shock waves (shock wave lithotripsy) combined with a pill that dissolves the remaining stone fragments. The treatment is safe and avoids the need for surgery in a specific group of patients. Although the risk of stone recurrence remains, shock wave lithotripsy may be repeated. I have been identified as being a possible candidate for either treatment.

The risks involved with surgery, and its general anaesthesia are very small and on average over 90% of patients will have no complications. About one patient in 200 may die from the surgery. Most patients will remain in the hospital for four to seven days after the operation. After discharge, a one month convalescent period because of pain at the incision site is usually required. Some of the more common post-operative complications include wound infection, atelectasis (a condition where part of a lung may not work for a short while), and venous thrombosis (when a clot forms in the veins of the legs).

Up to now, no deaths have been reported to be attributable to lithotripsy; however, after the treatment, some short lasting discomfort in the right upper abdomen may be felt in a few patients. Also, blood may appear in the urine for a few days. The procedure will be successful in about 70% of patients. Over 60% of patients will experience no further episodes of abdominal pain in the year following lithotripsy, although fragments will slowly be cleared from the gallbladder during this period, but about 1% of patients may develop pancreatitis, and 2% will go on to cholecystitis which requires the surgical removal of their gallbladder. The pill taken to make the gallstones dissolve may cause diarrhea in 4% of patients. Patients with unsuccessful lithotripsy results may then need surgery.

At present, since the better treatment alternative is unknown, and as the treatment of my gallstones is indicated, the type of therapy I receive will be decided by random assignment.

In order to assess the effectiveness of each treatment and the impact of gallstones on lifestyle, initial X-ray tests will be performed and follow-up gallbladder studies (ultrasounds every three months, and an X-ray every 6 months) will be performed over the next three years if I undergo lithotripsy. Whether I undergo surgery or lithotripsy, two small samples of blood will be drawn on two occasions during the month following the treatment as part of my routine care. I will fill out serial questionnaires characterizing my quality of life every three to six months at the time of follow-up visits; they should last no more than 15-20 minutes. All of the tests mentioned are usually part of follow-up care of patients after lithotripsy.

I understand that all information gathered in this study will remain confidential as required by law. My participation is voluntary, and I am free to refuse to participate, or to withdraw from participation at any time, without prejudicing my treatment.

The responsible physician at the Sir Mortimer B. Davis - Jewish General Hospital is Dr. Sigman (Tel.: 340-8287), and the patient representative is Roslyn Davlaso, RN (Tel.: 340-8200, ext. 5833).

As a part of the monitoring of hospital operations, a member of the Research Committee may contact me requesting that I answer questions about my participation. I will be free at the time to refuse to answer these questions.

I, the undersigned, have been given a copy of this consent form, and agree to participate in the McGill clinical project investigating the treatment of patients with

symptomatic gallbladder stones.

SIGNED:

DATE:

WITNESS:

GASTROINTESTINAL QUALITY OF LIFE (GIQL) SCALE

Troidl H, Eypasch E, Wood-Dauphinee S, Williams J I

CORE ITEMS

1. How often during the last 2 weeks have you been troubled by pain in the abdomen?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

2. How often during the last 2 weeks have you been troubled by a feeling of fullness in the upper abdomen?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

3. How often during the last 2 weeks have you been troubled by bloating (sensation of too much gas in the abdomen)?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

4. How often during the last 2 weeks have you been troubled by the excessive passage of gas?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

5. How often during the past 2 weeks have you been troubled by strong burping or belching?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

6. How often during the last 2 weeks have you been troubled by gurgling noises from the abdomen?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

7. How often during the last 2 weeks have you been troubled by frequent bowel movements?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

8. How often during the last 2 weeks has eating been a pleasure for you?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

9. Because of your illness, how often have you had to restrict the kinds of food you eat?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

10. During the last 2 weeks, how well have you been able to handle everyday stress?

( )	( )	( )	( )	( )
extremely poorly	poorly	moderately	well	extremely well

11. How often during the last 2 weeks have you felt sad about being ill?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

12. How often during the last 2 weeks have you felt nervous or anxious about your illness?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

13. How often during the last 2 weeks have you been happy with life in general?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

14. How often during the last 2 weeks have you felt frustrated about your illness?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

15. How often during the last 2 weeks have you been tired or fatigued?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

16. How often during the last 2 weeks have you felt unwell?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

17. Over the past week, how many nights have you woken up during the night?

( )	( )	( )	( )	( )
every night	5 to 6 nights	3 to 4 nights	1 to 2 nights	never

18. Since becoming ill, to what extent have you been troubled by changes in your appearance?

( )	( )	( )	( )	( )
a great deal	a moderate amount	somewhat	a little bit	not at all

19. Because of your illness, how much strength have you lost?

( )	( )	( )	( )	( )
a great deal	a moderate amount	somewhat	a little bit	none

20. Because of your illness, to what extent have you lost your endurance (the ability to keep doing an activity over time)?

( )	( )	( )	( )	( )
a great deal	a moderate amount	somewhat	a little bit	not at all

21. Because of your illness, to what extent do you feel unfit?

( )	( )	( )	( )	( )
extremely unfit	moderately unfit	somewhat unfit	a little unfit	feel fit

22. During the last 2 weeks, how often have you been able to complete your normal daily activities (school, work, household activities)?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

23. During the last 2 weeks, how often have you been able to take part in your usual leisure or recreational activities?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

24. During the last 2 weeks, how much have you been troubled by the medical treatment of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

25. To what extent have your personal relations with people close to you (family or friends) worsened because of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

26. To what extent has your sexual life been impaired (harmed) because of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

20. Because of your illness, to what extent have you lost your endurance (the ability to keep doing an activity over time)?

( )	( )	( )	( )	( )
a great deal	a moderate amount	somewhat	a little bit	not at all

21. Because of your illness, to what extent do you feel unfit?

( )	( )	( )	( )	( )
extremely unfit	moderately unfit	somewhat unfit	a little unfit	feel fit

22. During the last 2 weeks, how often have you been able to complete your normal daily activities (school, work, household activities)?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

23. During the last 2 weeks, how often have you been able to take part in your usual leisure or recreational activities?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

24. During the last 2 weeks, how much have you been troubled by the medical treatment of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

25. To what extent have your personal relations with people close to you (family or friends) worsened because of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

26. To what extent has your sexual life been impaired (harmed) because of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

ORGAN SPECIFIC ITEMS

1. How often during the last 2 weeks, have you been troubled by fluid or food coming up into your mouth (regurgitation)?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

2. How often during the last 2 weeks have you felt uncomfortable because of your slow speed of eating?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

3. How often during the last 2 weeks have you had trouble swallowing your food?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

4. How often during the last 2 weeks have you been troubled by urgent bowel movements?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

5. How often during the last 2 weeks have you been troubled by diarrhea?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

6. How often during the last 2 weeks have you been troubled by constipation?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

AUGUST 1992

Mon	Tue	Wed	Thu	Fri	Sat	Sun
					1	2
dose						
pain						
3	4	5	6	7	8	9
dose						
pain						
10	11	12	13	14	15	16
dose						
pain						
17	18	19	20	21	22	23
dose						
pain						
24	25	26	27	28	29	
dose						
pain						

In order to help us follow yor treatment, please note the days you skip doses of ursodeoxycholic acid by putting a mark (X) in the day along the line entitled "dose".
As well, on the days you experience the same type of pain than that attributed to your gallstones, please notify us at the phone numbers written on the front sheet, and write in the appropriate score on the line entitled "pain" according to the following scoring system:
Effect of the pain on your daily activities:
1.no change from normal
2.worked, but less than usual
3.missed work (or avoided domestic duties) because of the pain
4.sought medical advice because of the pain

Detailed costs of treatments

See tables 1-7

# of sessions per year	Amortization Period (yrs)		
	5	7	10
25	$1,050	$834	$672
50	$1,028	$818	$661
75	$1,008	$804	$651
100	$991	$792	$642

Table 1 Estimation of unit cost of lithotriptor and related supplies according to amortization period and number of cholelithiasis patients using it.

# of patients per year	Amortization period (yrs)		
	5	7	10
25	$701	$550	$437
50	$437	$361	$304
75	$348	$298	$260
100	$304	$267	$238

Table 2 Estimation of unit cost of laparoscopic equipment and related supplies according to amortization period and number of cholelithiasis patients using it.

Item	Unit cost	OPEN	LAP	LITHO
TOTAL		$374 ($174-$768)	$406 ($255-$854)	$341 ($274-$605)
Physician fees				
Evaluation visit	$71.50	1.00	1.00	1.00
Follow-up visit	$15.00	0	0	1.00
Consultations	$71.50	0.75	0.47	0.06
IMAGING				
Abdominal ultrasound	$23.07	0.92	1.44	1.24
Chest X-Ray	$35.88	0.88	1.07	0.97
Chest X-R mobile	$58.22	0	0.02	0
HIDA Scan	$60.00	0	0.07	0
IVP	$125.77	0	0.09	0
KUB	$15.43	0	0	1.12
Oral Cholangiogram	$41.03	0.13	0	1.00
PROCEDURE				
Colonoscopy	$212.50	0	0.05	0
ERCP	$135.25	0.08	0.09	0.06
Gastroscopy	$212.50	0.17	0.19	0.03
Pulmonary function	$137.00	0	0.02	0.00
TESTS				
Alkaline phosph.	$5.47	0.79	1.07	1.00
Amylase	$5.40	0.75	0.86	1.03
Anti-HBe	$11.31	0	0.05	0
Anti-HBc	$10.83	0	0.05	0
Anti-HBs	$10.83	0	0.05	0
Antibody-Screen	$25.45	1.08	1.00	0.06
AST	$7.66	0.96	0.86	0.73
Beta HCG	$4.85	0.29	0.49	0.42
Blood typing	$70.48	1.04	1.00	1.00
CBC	$8.11	1.04	1.40	1.09
Coombs	$15.67	0.13	0.09	0.03
ECG	$2.35	0.92	1.02	0.97
Hgb spot	$32.38	0	0	0.03
HBsAg	$11.31	0	0.05	0
Lipid Profile	$8.64	0	0	0.03
Prot. Electrophoresis	$16.34	0	0	0.03
PT/PTT	$6.35	1.00	0.65	1.00
Schilling test	$237.44	0	0	0.03
SMAC	$5.47	1.08	1.40	1.15
Urinanalysis	$4.54	0.42	0.65	1.00

Table 3 Costs of evaluation.

		OPEN	LAP
TOTAL		$2,739	$2,089
Average cost of supplies			$361
TOTAL		$2,739	$2,450
Max		$4,298	$4,200
Min		$1,983	$1,588
			135.74
Anesth.Time(min)	$0.67	107.42	
Consultation	$72.00	0.00	0.26
Fee Chole	$354.98	1.00	1.00
Litho fee	$114.99	0.00	0
Pre-Anesth.ASSESS.	$43.00	1.00	1.00
HOSPDUR (days)	$331.71	4.35	2.48
Home care(1h)	$0.00	0.83	0.00
ICU hours	$30.14	1.00	0.00
LITHO ROOM	$271.00	0.00	0
Litho room	$271.00	0.00	0
OPTIME (min)	$5.90	70.58	86.95
Recovery R(hours)	$15.55	2.41	1.98
TOTSTAY1	0	0.00	0
Abd.X-Rays series	$51.33	0.17	0.07
Abdom.US	$23.07	0.00	0.07
Chest X-Rays	$58.22	0.29	0.07
HIDA SCan	$60.00	0.04	0.05
IOPCHOL	$114.63	0.17	0.05
Arterial Line	$15.00	0.08	0.00
Echocardiogram	$22.85	0.00	0.02
Art.blood gases	$13.14	0.42	0.14
Bile culture	$24.39	1.29	0.84
CBC	$8.11	1.38	0.28
ECG	$2.35	0.25	0.07
PT/PTT	$6.35	0.00	0.19
Pathology	$18.28	1.08	1.00
Pulm.Function	$137.00	0.00	0.02
SMAC	$5.47	1.46	0.37
Typing blood	$70.48	0.00	0.12
Urinanalysis	$4.54	0.58	0.21
Uro culture	$0.03	0.00	0.02
Wound culture	$22.47	0.08	0.00
Antibody screen	$25.45	0.00	0.12

Table 4 Costs of the surgical strategies

Description	Unit cost	OPEN	LAP
Acetaminophen (mg)	$0.01	535.42	159.77
Adalat(mg)	$0.44	3.33	0.23
Ativan (mg)	$0.01	0.81	0.60
Atracurium	$37.10	0.58	0.27
Atropine	$2.00	0.46	0.32
Brietal	$26.43	2.50	0.00
Cefoxitin (1g)	$11.50	0.13	0.00
Cephazoline	$2.65	1.58	1.63
Codeine	$0.18	15.00	5.58
DTC	$1.05	0.39	3.26
Diazide (mg)	$0.28	5.21	0.00
Diovol (mL)	$0.16	2.50	0.00
Diprivan	$0.00	0.00	8.14
Droperidol(mg)	$4.85	0.74	0.87
Empracet (mg)	$0.02	107.50	128.84
Fentanyl (ug)	$0.08	221.88	328.49
Flaxedil	$3.96	0.00	0.47
Glycer.Suppos.(unit)	$0.08	0.33	0.19
Glycopyrolate(mg)	$47.65	0.22	0.40
Gravol (mg)	$0.12	59.81	42.33
Heparin (UI)	$0.00	2083.33	1767.44
Labetalol	$17.32	0.00	0.12
Lanoxin (mg)	$12.08	0.10	0.00
MOM (mL)	$1.11	10.00	0.00
Meperidine (mg)	$0.00	413.54	72.67
Metamucil (cc)	$0.11	3.75	0.70
Midazolam (mg)	$0.46	0.09	0.81
Morphine (mg)	$0.29	22.58	8.92
Neostigmine(mg)	$1.50	1.41	1.94
Nubaine(mg)	$17.52	0.00	0
Pancuronium (mg)	$0.99	1.67	1.95
Phenergan	$0.01	9.38	6.40
Propanolol	$5.38	0.00	0.47
Regonal (mg)	$0.57	0.42	0.00
STP	$2.10	0.00	0.00
Sectral(mg)	$0.31	8.33	0.00
Serax (mg)	$0.10	1.25	0.00
Stemetil (mg)	$0.53	0.83	0.00
Sux	$0.68	36.67	50.93
Tenormin (mg)	$0.00	8.33	0.00
Tensilon (mg)	$0.09	1.46	0.00
Thiopental (mg)	$0.00	360.21	312.21
Valium (mg)	$0.42	2.71	2.62
Vecuronium (mg)	$1.82	4.02	3.41

Table 5 Costs of medications used during surgical hospitalizations.

Type of use	# OF TABS	MAX	MIN	AVERAGE COST
ALL				
Use continued	934	2163	0	$1,120
Use stopped	438	1512	0	$526
Use all	630	2163	21	$756
3 LITHOS				
Use continued	1065	2163	480	$1,278
Use stopped	719	1512	98	$863
Use all	927	2163	98	$1,112
2 LITHOS				
Use continued	880	1345	414	$1,055
Use stopped	410	748	21	$492
Use all	598	1345	21	$718
1 LITHO				
Use continued	763	1268	506	$916
Use stopped	351	995	26	$421
Use all	454	1268	26	$545

Table 6 Cost of the litholytic agent

Follow-up Costs			
period (m)	OPEN	LAP	LITHO
1	$12	$13	$51
3	$8	$7	$35
6	$9	$6	$36
9	$3	$2	$45
12	$6	$2	$48
15	$7	$2	$8
18	$38	$0	$62
TOTAL	$83	$32	$284

Table 7 - Follow-up costs according to treatment