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Jukka Harju

Minilaparotomy Cholecystectomy in the Treatment of Gallstone Disease

Comparison with Laparoscopic Cholecystectomy

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ABSTRACT:

Laparoscopic cholecystectomy is the gold standard of treatment of elective symptomatic gallstone disease. Laparoscopic surgery requires special equipment, and there is probably a longer learning curve in laparoscopic procedures than in open techniques. Laparoscopic surgery has an obvious benefit in postoperative recovery compared with standard open surgery. This has lead to a search for minimally invasive open techniques with similar or even better results and probably a shorter learning curve without expensive disposable equipment. The aim of this thesis work was to evaluate (i) the efficacy and safety and (ii) the feasibity of minilaparotomy cholecystectomy as a day case surgery in patients with symptomatic gallstones disease. A total of 335 patients (188 in the minilaparotomy groups and 147 in the laparoscopic groups) were evaluated in 4 studies and the results are presented in 6 publications.

In a pivotal prospective clinical study symptomatic patients with gallstones were randomised to minilaparotomy (n=85) or laparoscopic groups (n=72). The mean operative time was statistically significantly shorter in the minilaparotomy group than in the laparoscopic group (mean: 55min SD 20 vs. 79min SD 27, p=0.0001). There were no significant differences in postoperative pain, analgesic consumption, or postoperative pulmonary function. Obesity did not have a statistically significant influence in either group.

The patients were re-evaluated 4 weeks postoperatively using the RAND-36 quality of life questionnaire. The laparoscopic procedure was slightly better in the role functioning/physical measure (63 vs. 49, p=0.038, scale 0-100), but in every other parameter there was no difference between the two groups.

A phone interview was used to evaluate the long-termoutcomes of the study. The mean follow-up time was 10 years, and 81% of the patients were reached in both groups (n=69 in the minilaparotomy and n= 58 in the laparoscopic group). The prevalence of chronic post-surgical pain was similar in the two groups, 5/69 (7%) in the minilaparotomy group and 1/58 (2%) in the laparoscopic group (p=0.14), respectively. Residual abdominal symptoms were common, but less frequent in the minilaparotomy group (14/69; 20%) than in the laparoscopic group (21/58 patients; 36%) (p=0.039). In the minilaparotomy group 63/69 patients (91%) and 57/58 patients (98%) in the laparoscopy group (p=0.059) were satisfied with the cosmetic outcome.

To evaluate the applicability of minilaparotomy for day surgery, a pilot study with 30 prospective patients was carried out. Day surgery was possible in 25 cases (83%). Four patients out of five who stayed overnight at the hospital had an incision longer than 7 cm,

and all of them had a body mass index over 30 kg/m^2. After the pilot study, altogether 60 patients were randomised to day surgery cholecystectomy (n=29 in minilaparotomy and n=31 in laparoscopic group). The success rate as a day surgery for minilaparotomy was 66% (19/29) and for laparoscopy 55% (17/31), with no difference between the two groups. Chronic cholecystitis, postoperative nausea and vomiting were significant variables associated with failure in day surgery.

To improve the minilaparotomy technique 44 patients were operated with ultrasonic scissors and this technique was compared with the conventional laparoscopy (n=44). Patients in the minilaparotomy group had significantly less postoperative pain than the laparoscopic group (the area under the time curve for pain for 0-5 hours: 8 (6) vs. 14 (9), respectively, p=0.002. The convalescence needed was 3 days shorter in the minilaparotomy group, 7 (3) days, than in the laparoscopic group, 10(8) days, (p=0.024).

Based on these data it is concluded that in the treatment of symptomatic gallstone disease the minilaparotomy cholecystectomy is as good as conventional laparoscopic cholecystectomy when short-term or long-term outcomes are considered. Ultrasonic dissection in minilaparotomy cholecystectomy seems to improve short-term outcome compared with laparoscopic cholecystectomy using the conventional electrosurgical technique.

National Library of Medicine Classification: WI 750, WI 755, WI 900, WO 192
Medical Subject Headings: Laparotomy; Cholecystectomy/methods; Cholecystectomy, Laparoscopic, Laparoscopy; Ambulatory Surgical Procedures; Gallstones/surgery

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TIIVISTELMÄ:

Tähystysteitse tehtävä sappileikkaus on pääasiallinen leikkausmenetelmä hoidettaessa oireilevia sappikiviä. Tähystysleikkauksen tekeminen vaatii erikoisvälineistöä ja tähystystoimenpiteiden oppiminen saattaa kestää kauemmin kuin vastaavan avoleikkauksen. Perinteisiin avoleikkauksiin verrattuna potilaiden toipuminen tähystysleikkauksen jälkeen on yleensä nopeampaa. Avoleikkauksiakin on mahdollista tehdä potilaaseen vähemmän kajoavalla tavalla, jolloin kalliita tähystysleikkausvälineitä ei tarvita ja leikkauksen oppiminen voi olla nopeampaa.

Tämän väitöskirjan tarkoituksena oli arvioida (i) miniviiltosappileikkauksen tehokkuutta ja turvallisuutta ja (ii) leikkausmenetelmän soveltuvuutta päiväkirurgiaan potilailla, joilla on oireita aiheuttavia sappikiviä

Yhteensä 355 potilasta (188 miniviiltoleikkausryhmässä ja 147 tähystysleikkausryhmässä) arvioitiin neljässä erillisessä tutkimuksessa ja tulokset julkaistiin kuutena julkaisuna.

Keskeisessä kliiniseen seurantatutkimukseen satunnaistettiin oireista sappikivitautia sairastavia potilaita miniviilto (n=85) ja tähystysleikkaus (n=72) ryhmiin. Keskimääräinen leikkausaika oli tilastollisesti merkitsevästi lyhyempi miniviiltoryhmässä kuin tähystysleikkausryhmässä (ka 55 min; SD: 20 vs. 79 min; SD 27, p=0,0001). Leikkauksen jälkeisessä kivussa, kipulääkkeiden kulutuksessa tai hengitystoiminnoissa ei ryhmien välillä ollut eroa. Lihavuus ei vaikuttanut tuloksiin kummassakaan ryhmässä.

Potilaille tehtiin 4 viikkoa leikkauksen jälkeen RAND-36 elämänlaatukysely. Tähystysleikkausryhmässä Roolitoiminta/fyysinen oli hieman parempi kuin miniviiltoleikkausryhmässä (63 vs. 49, p=0,038, asteikko 0-100). Muissa muuttujissa ei elämänlaatutestissä ollut eroa ryhmien välillä.

Pitkäaikaistuloksia kyseltiin potilailta puhelinhaastattelulla. Keskimääräinen seuranta-aika oli 10 vuotta ja 81% molemmista ryhmistä tavoitettiin haastatteluun (n=69 miniviiltoryhmässä ja n=58 tähystysleikkausryhmässä) Pitkäaikaista leikkaushaava-alueen kipua oli viidellä (5/69, 7%) miniviiltoleikatulla potilaalla ja yhdellä (1/58, 2%) tähystysleikatulla potilaalla, mutta ryhmien välillä ei ollut tilastollista eroa. Vatsaoireet olivat yleisiä molemmissa ryhmissä, mutta tähystysleikatuilla oli tilastollisesti merkitsevästi enemmän oireita kuin miniviillolla leikatuilla (36% 21/58 vs. 20% 14/69, p=0,039) Miniviiltoryhmässä 63/69 (91%) ja tähystysleikkausryhmässä 57/58 (98%) potilaista oli tyytyväisiä leikkauksen lopputulokseen, mutta ero ei ollut tilastollisesti merkitsevä (p=0,059).

Miniviiltoleikkauksen sopivuutta päiväkirurgiaan tutkittiin kolmenkymmen potilaan pilottitutkimuksella. Päiväkirurgia onnistui 25 potilaalla (83%). Kaikki potilaat, joilla päiväkirurgia ei onnistunut, olivat ylipainoisia (painoindeksi yli 30 kg/m^2) ja heistä neljällä miniviiltoa jouduttiin suurentamaan tai vatsalihaksia katkaisemaan. Pilottitutkimuksen jälkeen 60 potilasta satunnaistettiin miniviilto (n=29) ja tähystysleikkaus (n=31) ryhmiin. Miniviiltoryhmässä päiväkirurgia onnistui 66%:lla (19/29) ja tähystysryhmässä 55%:lla

(17/31). Pitkäaikainen sappirakon tulehdus, leikkauksen jälkeinen pahoinvointi tai oksentelu olivat merkittävimmät syyt päiväkirurgian epäonnistumiseen.

Miniviiltoleikkauksen kehittämiseksi 44 potilasta leikattiin satunnaistetussa kliinisessä tutkimuksessa ultraäänisaksilla ja potilaita verrattiin tavanomaisella tähystysleikkauksella (n=44) leikattuihin potilaisiin. Miniviiltoryhmän potilailla oli vähemmän leikkauksen jälkeistä kipua kuin tähystysleikkausryhmässä (kipu-aika-käyrän alainen pinta-ala 0-5 h leikkauksesta 8 (6) vs. 14 (9) p=0,002). Miniviiltoryhmässä sairausloman tarve oli 3 vuorokautta lyhyempi kuin tähystysleikkausryhmässä: 7 (3) vs. 10 (8), p=0,024.

Tämän tutkimuksen perusteella voidaan todeta, että oireilevan sappikivitaudin hoidossa miniviiltoleikkaus vaikuttaisi olevan yhtä hyvä kuin tavanomainen tähystysleikkaus sekä lyhyt- että pitkäaikaistulosten osalta. Käytettäessä ultraäänisaksia potilaat ovat miniviiltoleikkauksen jälkeen kivuttomampia ja toipuvat leikkauksesta nopeammin kuin tavanoimaisella tähystysleikkauksella leikatut.

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Jukka Harju

List of the original publications

This dissertation is based on the following original publications:

I Harju J, Juvonen P, Eskelinen M, Miettinen P, Pääkkönen M. Minilaparotomy cholecystectomy versus laparoscopic cholecystectomy: a randomized study with special reference to obesity. *Surg Endosc 20: 583-586, 2006.*

II Harju J, Pääkkönen M, Eskelinen M. Comparison of the quality of life after minilaparotomy cholecystectomy versus laparoscopic cholecystectomy: a prospective randomized study. *Isr Med Assoc J 9: 147-148, 2007.*

III Harju J, Pääkkönen M, Eskelinen M. Minilaparotomy cholecystectomy as a day surgery procedure: a prospective clinical pilot study. *Scand J Surg 96: 206-208, 2007.*

IV Harju J, Kokki H, Pääkkönen M, Karjalainen K, Eskelinen M. Feasibility of minilaparotomy versus laparoscopic cholecystectomy for day surgery: a prospective randomised study. *Scand J Surg 99: 132-136, 2010.*

V Harju J, Aspinen S, Juvonen P, Kokki H, Eskelinen M. Ten-year outcome after minilaparotomy versus laparoscopic cholecystectomy: a prospective randomized trial. *Surg Endosc 27: 2512-2516, 2013.*

VI Harju J, Juvonen P, Kokki H, Remes V, Scheinin T, Eskelinen M. Minilaparotomy cholecystectomy with ultrasonic dissection versus laparoscopic cholecystectomy with electrosurgical energy: a randomized multicenter study. *Scand J Gastroenterol. 48: 1317-1323, 2013.*

Contents

Abbreviations

BMI	body mass index
CBD	common bile duct
CSQ	condition specific questionnaire
ERCP	endoscopic retrograde cholagiopancreatography
ESWL	extracorporeal shock wave lithotripsy
LC	laparoscopic cholecystectomy
MC	minilaparotomy cholecystectomy
MRI	magnetic resonance imaging
NOTES	natural orifice transluminal endoscopic surgery
NRS	numeric rating scale
VAS	visual analogue scale

1 Introduction

Cholecystectomy is a common surgical procedure. There were 7 935 cholecystectomy operations performed in Finland in the year 2011, and 6 695 of them were performed laparoscopically. Cholecystectomy was the second most common operation in gastroenterological surgery after operation for inguinal hernia in Finland in the same year. (Rautiainen H et al 2012)

Gallstones constitute a significant health problem in developed societies, affecting 10% to 15% of the adult population. Up to 80%, however, will never experience biliary pain or complications such as acute cholecystitis, cholangitis, or pancreatitis. Many gallstones are clinically symptomless, an incidental finding often uncovered during abdominal ultrasound performed for another reason. (Stinton LM et al 2012)

The aetiology for gallstones is multi-factorial. There are genetic factors and environmental reasons for gallstones. Chronic over-nutrition with carbohydrates, depletion of dietary fibres and a 'westernised' high-fat diet seems to increase the risk for developing gallstones. (Stokes CS et al 2011)

Carl Langenbuch, a German doctor, was the first surgeon who successfully removed a gallbladder from a human being in 1882 (Traverso LW 1976). Since then open cholecystectomy was the only procedure to operate gallstone disease for more than one hundred years. In 1985 Eric Mühe (1986) performed the first laparoscopic cholecystectomy. Mühe was strongly derided and criticized at first, but by the beginning of the 1990's laparoscopic cholecystectomy had spread rapidly over the world. However, this enthusiasm was not based on evidence from prospective randomized studies comparing open cholecystectomy and laparoscopic cholecystectomy (Cuschieri A 1991, Jani K et al 2006). The advance of laparoscopy compared to conventional techniques was assumed so obvious that surgeons did not wait for results from randomized studies. This new technique was also adopted in Finland very soon, and the first laparoscopic cholecystectomy was performed in the autumn in 1990 (Ovaska J and Kivilaakso E 1994).

The development of the laparoscopic surgery has continued during the last two decades. Laparoscopic cholecystectomy trough single incision has inspired many surgeons (Romanelli JR et al 2008), even though it seems that a slightly better cosmetic result is its only benefit (Lai EC et al 2011, Pan MX et al 2013).

The latest innovation is a so-called 'natural orifice transluminal endoscopic surgery' (NOTES) (Clark MP et al 2012), where cholecystectomy is performed through the vagina or the stomach. But accepting it as a common practice has been very contradictory (Kobiela J et al 2011).

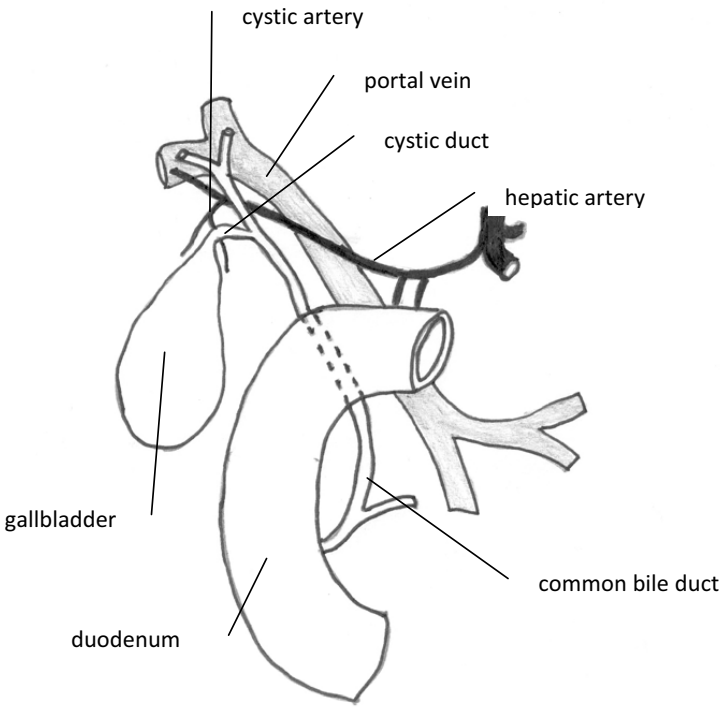
As the laparoscopic technique began its triumph over the world, there were some surgeons who changed their technique in open surgery and started to do open cholecystectomy trough a small incision (minilaparotomy), with good results (Ledet WP 1990). The purpose of this thesis was to evaluate the efficacy and safety of minilaparotomy cholecystectomy compared to laparoscopic cholecystectomy.

2 Review of the literature

2.1 ANATOMY OF THE GALLBLADDER AND BILIARY TREE

The liver parenchyma and blood vessels form small liver units, liver lobules, from where small bile ducts also originate. Inside the liver small branches of bile ducts joint together and form the left and right hepatic bile ducts. In the porta hepatis the left and right branches form the common hepatic duct. The common hepatic duct is 4 to 6 cm long. At the junction of the cystic duct it turns into the common bile duct (CBD), which goes through the pancreas and ends penetrating the duodenal wall in the major duodenal papilla. The gallbladder is joined together to the biliary tree by the cystic duct. The gallbladder is a pear-shaped, thin-walled 8 to 12 cm long bag that lies in the fossa of the liver attached by connective tissue. The lumen of the neck of the gallbladder and its connection with the cystic duct is incompletely subdivided by a spiral diaphragmatic fold of mucosa. The gallbladder receives its blood supply from the cystic artery deriving from the hepatic artery, which is a branch of the common hepatic artery. The common hepatic artery originates from the coeliac trunk. (Kahle W et al 1986) The most common anatomy of the extra hepatic bile ducts and the gallbladder are shown in picture 1.

Although the anatomy of the gallbladder and extra hepatic biliary tree is generally undisputable, there are many variations in the anatomy of the cystic duct and artery, which are important to detect especially when cholecystectomy is performed. (Lamah M et al 2001, Ding YM et al 2007)



Picture 1. Anatomy of extrahepatic bile ducts and gallbladder.

2.2 GALLSTONE DISEASE

2.2.1 Epidemiology

Gallstones are a common problem in developed countries. Gallstones are found in 10% to 15% of the adult population, but only about 20% of people with stones develop any biliary pain or complications such as acute cholecystitis, cholangitis or pancreatitis. The mortality rate for gallstone disease is relatively low at 0.6%. Women are twice as likely to develop gallstones as men. Some of the risk factors for cholesterol gallstones are not modifiable, for example ethnic and genetic background, increasing age and female gender. Modifiable risk factors include obesity, rapid weight loss, sedentary lifestyle and long-erm parenteral nutrition. Certain situations where there is stasis in the gallbladder (spinal cord injury or use of drugs such as somatostatin) increase the risk for gallstones. Incremental obesity might increase the prevalence of cholesterol gallstones. In the United States there are an estimated 1.8 million visits in hospitals per year due to gallstone disease. In most of cases the visits are ambulatory and do not require overnight admission. (Stinton LM et al 2010 and 2012)

In Finland cholecystectomy is the second most common operation in gastroenterological surgery after inguinal hernia operation. In 2011 there were 7935 gallbladder operations, which needed 19357 days of hospitalisation. The mean number of hospitalisation days after cholecystectomy was two days and median one day. The mortality rate was 0.2%, which is lower than in the United States. (Rautiainen H et al 2012)

2.2.2 Aetiology and pathogenesis of gallstones

Gallstone formation is a complex process that depends on genes and environmental factors. Gallstones can be divided into two main groups: cholesterol stones and pigment stones. In Finland 90 % of gallstones are cholesterol stones. In cholesterol gallstone formation supersaturated bile is essential. The pathology of cholesterol gallstones is not fully understood and there are healthy people with supersaturated bile without gallstones. It seems that a disturbance in the crystallization of bile and emptying of the gallbladder is needed. Obesity, rapid loss of weight, elevated serum triglycerides and consumption of alcohol all increase the risk for developing gallstones. (Kiviluoto T et al 2007, Marschall HU et al 2007 and 2010, Venneman NG et al 2010, Banim PJ et al 2011) According to the cohort study by Banim PJ et al (2010), increasing physical activity might decrease the development of symptomatic gallstones.

Pigment gallstones are classified as 'black' or 'brown'. They are composed mostly of calcium hydrogen bilirubinate, which is oxidised in 'black' stones, but remain unpolymerised in 'brown' stones. Black stones form in sterile gallbladder, but brown stones form secondary to stasis and bacterial infection in the biliary tree. Black pigment stones may form because of haemolysis or ineffective erythropoesis. (Vitek L and Carey MC 2012)

2.3 DIAGNOSTICS OF GALLSTONE DISEASE

2.3.1 Patients history and questionnaires

About one tenth of the population in developed countries has gallstones, but only one fifth of them ever experiences symptoms from gallstones. How can we find those patients whose symptoms are due to gallstones? In Italy Festi D et al (1999) carried out a large population-based cross-sectional study, in which they found out that pain in the epigastrium and even moreso pain in the right hypochondrium were significantly associated with gallstones. Especially epigastric and hypochondric pain after fried or fatty food without symptoms of heart burn were associated with gallstones. Berger MY et al (2004) performed a prospective cohort study consisting of 233 patients. In their study there was no causal relationship between suspected gallstone symptoms and gallstones. Mertens MC et al (2010) carried out a prospective consecutive study with 172 patients undergoing laparoscopic cholecystectomy predicting factors for persisting symptoms after cholecystectomy. In their study six months after cholecystectomy the patients with only typical biliary symptoms were most often free of symptoms (63%). Patients with preoperative dyspeptic symptoms and psychotropic medications had a 4-5 times higher risk for the persistence of pre-existing pain and other symptoms after cholecystectomy: 63% of patients with preoperative dyspeptic symptoms reported persisting symptoms at 6 months.

Questionnaires may be helpful in identifying what kind of an impact the symptoms originating from gallstones may have on the quality of life. Chen TY et al (2006) used The Otago gallstones condition-specific questionnaire (CSQ) for patients with gallstones. The questionnaire was designed based on a review of published reports, structural equation modelling (physical functioning, systemic functioning, social functioning and emotional functioning), input from experts and patient feedback. They found that the CSQ was clinically relevant when showing the relationship with surgeon-rated priority. According to their study, the CSQ could be valuable in helping surgeons make priority decisions in addition to tracking subsequent outcomes.

2.3.2 Physical examination

A normal gallbladder is not palpable. A palpable gallbladder with jaundice often means there is malignant reason for it (carcinoma of the pancreas or biliary tree) or sometimes there can be another chronic obstruction in the biliary tree (inflammation or stones). If the obstruction is above the cystic duct, it does not cause a palpable gallbladder. (Munzer D 1999, Fitzgerald JE et al 2009) Chronic obstruction in the cystic duct may dilate the gallbladder without jaundice. Inflammation is often associated with gallstones, and ischaemia of the gallbladder can lead to transmural calcification and develop into a so-called porcelain gallbladder which might be palpable (Khan ZS et al 2011).

In case of acute cholecystitis, Murphy's sign might be positive. It is tested during an abdominal examination by asking the patient to breathe out and then placing the hand below the right costal margin at the mid-clavicular line. The patient is then instructed to inspire, and if they stop breathing in and wince and hold their breath, the test is considered positive. (Adedeii OA and McAdam WA 1996)

2.3.3 Laboratory tests

Laboratory tests are usually normal if gallstones do not cause any obstruction or other complications. Mirizzi syndrome is a rare condition, where the gallstones in the gallbladder induce mechanical compression to the common bile duct. Hyperbilirubinaemia is the most common laboratory finding among the Mirrizzi syndrome patients. Other laboratory abnormalities are elevated aminotransaminase concentrations and leucocytosis. The malignancy marker, Ca19-9, might also be highly elevated without biliary tract cancer. (Waisberg J et al 2005, Beltran MA 2012)

Hyperbilirubinaemia and elevated alkaline phosphatase predict gallstones in the common bile duct, if the patient has a history of gallstone disease. In addition, elevated aspartate aminotransferase and alanine aminotransferase might be predictors of choledocholithiasis. (Stain SC et al 1994, Abboud PA et al 1996, , Shiozawa S et al 2005, Al-Azawi D et al 2007, Pourseidi B and Khorram-Manesh A 2007, and Notash AY et al 2008)

2.3.4 Imaging modalities

Gallstones may be visible on plain x-ray, if they contain enough calcium, which is possible in 15-20% of cases. Therefore plain radiography is a poor method for screening gallstones. After

1924 oral cholecystography was the main radiographic imaging modality for gallstones for decades, but it is rarely used nowadays. Ultrasound has replaced oral cholecystography during the last three decades. Ultrasound offers several advantages: it is highly sensitive (>95%) and accurate, it is non-invasive without ionizing radiation, it is relatively cheap, and it has the ability to evaluate adjacent organs. (Bortoff GA et al 2000)

If an ultrasound examination fails to demonstrate gallstones, a cholescintigraphy scan can be performed as a supplemental examination. Cholecystoscintigraphy is highly sensitive in the diagnosis of acute cholecystitis, but it does not provide information on adjacent organs. In the cholescintigraphy scan a radioactive tracer is injected intravenously and allowed to circulate to the liver, where it is excreted into the biliary system and stored by the gallbladder and the biliary system. However, the cholescintigraphy scan is rarely used and it is not done as first line due to increased cost and invasiveness. (Shea JA et al 1994, Bortoff GA et al 2000)

Computed tomography is a useful as an adjunctive imaging modality when ultrasound results are equivocal or the clinical setting suggests disease of adjacent organs (e.g. pancreatitis). It can demonstrate gallbladder wall thickening, gallstones (depending on composition), pericholecystic inflammation, and pericholecystic abscess. In computed tomography patients are exposed to ionizing radiation and not all gallstones are visible in this examination. (Bortoff GA et al 2000)

Magnetic resonance imaging (MRI) has essentially no role as a primary imaging modality for detection of gallstones in the gallbladder, but it is important in the evaluation of associated complications (e.g. acute cholecystitis, pancreatitis, and biliary obstruction). In gallstone detection MRI's sensitivity is approximately 90 – 95% and stones in the CBD can be detected with much greater sensitivity than with ultrasound. (Bortoff GA et al 2000)

Endoscopic retrograde cholangiopancreatography (ERCP) was the standard of reference for detection of CBD stones, but MRI has replaced ERCP as first line imaging modality for CBD stones. ERCP is an invasive operation with a risk of complications and it exposes the patient to ionizing radiation. ERCP is therefore reserved for therapeutic intervention rather than a diagnostic tool. (Becker CD et al 1997, Bortoff GA et al 2000)

2.3.5 Differential diagnosis

There are several reasons for acute or chronic abdominal pain other than gallstones. Miettinen P et al (1996) carried out a prospective study with a total of 639 patients admitted to a university hospital emergency room for acute abdominal pain. The most common cause of acute abdominal pain was non-specific abdominal pain (33.0%). Acute appendicitis was the second most common reason (23.3%) for abdominal pain, and acute biliary disease (e.g. gallstone colic or acute cholecystitis) the third most common (8.8%) reason. In the male population alcoholic pancreatitis and gastritis, renal stones and peptic ulcers were also common. In acute abdominal pain other causes must also be remembered (e.g. heart attack, aortic aneurysm rupture, acute visceral ischaemia). In the case of acute abdomen computed tomography is a good imaging modality for diagnosis (Systermans BJ and Devitt PG 2013). When peptic ulcer disease is suspected as a cause of abdominal pain, gastroscopy is essential (Malfertheiner P et al 2009).

2.4 INDICATIONS AND TIMING FOR TREATMENT OF GALLSTONES

Most gallstones are asymptomatic and discovered incidentally in an abdominal ultrasound or an autopsy. The classical symptoms of gallbladder gallstones are right upper quadrant or epigastric pain. The pain may radiate to the back or the right scapula and typically develops rapidly after fatty or fried food. In a complicated situation gallstones may develop acute or chronic cholecystitits, acute cholangitis and pancreatitis. All these above-mentioned symptoms or complications are widely accepted indications for the treatment of gallstones. (Attili AF et al 1995)

Is it necessary to do cholecystectomy at the time of admission for acute cholecystitits or should surgery be delayed (more than six weeks after index admission)? Gurusamy KS et al (2013) analysed in a Cochrane Database Systematic review six trials involving a total of 488 patients who had acute cholecystitis and were fit to undergo laparoscopic cholecystectomy. Patients were randomised to early laparoscopic cholecystectomy (n=244) or delayed laparoscopic cholecystectomy (n=244). There were no significant differences between the groups in the primary outcomes, but in the early laparoscopy group the total length of stay in hospital appeared shorter.

Gallstones are the second most common reason for acute pancreatitits. If the gallbladder is not removed, pancreatitits may renew. However, the safety of cholecystectomy has been questioned. Tang E et al (1995) showed that early laparoscopic cholecystectomy is safe to perform after mild acute pancreatitis, but if pancreatitis is not mild, an early operation may increase operative complications and rate of conversions, as well as lengthen postoperative stays. Falor AE et al (2012) have confirmed in a retrospective study (n=303) that in mild pancreatitis there is no need to delay cholecystectomy, and it can be safely performed within 48 hours of the hospital admission.

Since most of the gallstones found in the gallbladder never cause symptoms, they do not require any treatment before they become symptomatic. However, there are some exceptions when the treatment of asymptomatic gallstones should be considered. There is an association between gallbladder cancer and gallstones. Cancer in the gallbladder is very rare, but the prognosis is poor and therefore asymptomatic gallstones might be an indication for surgery especially in areas where gallbladder carcinoma is common. (Batra Y et al 2005) If a patient suffers from a chronic haemolytic syndrome (e.g. sickle cell disease), there is an increased risk for developing symptoms of gallstones, and emergency surgery among those patients is associated with higher morbidity, mortality and increased hospital stay. Thus elective prophylactic cholecystectomy is recommended before the development of symptoms. (Curro G et al 2007) If a patient is waiting for organ transplant surgery, it has traditionally been an indication to operate asymptomatic gallstones, as some immunosuppressive drugs are prolithogenic and immunosuppression might mask symptoms and signs of acute cholecystitis. According to recent studies it seems that the expectant management of asymptomatic gallstones does not increase mortality and morbidity among organ transplantation patients. (Sianesi M et al 2005, Jackson T et al 2005, Takeyama H 2006)

In the past it was thought that asymptomatic gallstones should be operated if a patient has diabetes mellitus. It was thought that diabetic patients are at a higher risk for developing complications and there is a higher morbidity and mortality among those patients. However, it seems that diabetic patients with asymptomatic gallstones are not at a higher risk for gallstones

complications. Thus a wait-and-see policy is reasonable, but early surgery is recommended if diabetic patients develop cholecystitis. (Landau O et al 1992, Aucott JN et al 1993, Babineau TJ and Booth A Jr 1995)

Patients with liver cirrhosis have been documented to have a decreased risk for the formation of gallstones but most of these patients are asymptomatic. If cirrhosis is in an advanced stage, there is a higher risk for complications with gallstone surgery. Because asymptomatic gallstones are at a low risk of developing symptoms and the risks for complications with surgery are elevated among cirrhotic patients, prophylactic cholecystectomy is not recommended. (Dunnington G et al 1987, Orozco H et al 1994)

Cholecystitis may sometimes develop without gallstones. That condition is called acute acalculous cholecystitis. It is a serious complication of critical illness (e.g. infection, long intensive care unit stay, and multiple organ failure). Even though patients with acute acalculous cholecystitis are critically ill, it seems that cholecystectomy is the treatment of choice, but percutanous ultrasound-guided drainage has also been used. (Laurila J et al 2004)

2.5 CONSERVATIVE TREATMENT

Cholecystectomy is the standard and definitive treatment for symptomatic gallbladder stones and can be performed regardless of the type, number, and size of the stones. In special situations, however, oral dissolution therapy for gallstones has been used in a limited patient population. If gallstones are smaller than 15 mm and the gallbladder is functioning normally, dissolution therapy might be considered if operative treatment is not possible. Ursodeoxycholic acid has been used for several years for the dissolution of gallstones. Ursodeoxycholic acid is a bile salt that reduces the secretion of cholesterol into bile and increases cholesterol solubility. It may also improve gallbladder emptying. Treatment should continue for several months and approximately 25% of the patients develop recurrent gallstones within five years. (Bellows CF et al 2005)

Cholesterol lowering agents that inhibit hepatic cholesterol synthesis (statins) or intestinal cholesterol absorption (ezetimibe), or drugs acting on specific nuclear receptors involved in cholesterol and bile acid homeostasis may offer additional medical therapeutic tools for treating cholesterol gallstones. The role of these medications in treating or preventing gallstones has not been established. (Wang HH et al 2008, Wang HH et al 2009, Di Ciaula A et al 2010)

Extracorporeal shock wave lithotripsy (ESWL) was succesfully used in 1985 for gallbladder stones (Sauerbruch T et al 1986). Although ESWL was a very promising method in the beginning, the risk of recurrence stones is very high, and long-term results are unsatisfactory (Carrilho-Ribeiro L et al 2006). Nowadays ESWL has limited role in treatment of selected patients with pancreatic or large common bile duct stones (Tandan M and Reddy DN 2011)

In certain situations seriously ill patients with an acute cholecystitits are not fit enough for surgery. In those situations percutaneous cholecystectomy is an option. Percutaneous cholecystectomy can be a bride to subsequent definitive surgery or in selected cases a definitive solution. (Nikfarjam M et al 2013)

2.6 OPERATIVE TREATMENT

2.6.1 Conventional open cholecystectomy

After Carl Langenbuch described the first successful cholecystectomy in 1882, not much changed in the operation techniques during the following decades. In 1915 Edward Starr Judd published an illustrated article about cholecystectomy in the Annals of Surgery and that technique is very similar to open cholecystectomy nowadays. According to Judd, cholecystectomy is best accomplished from below upward (antegrade technique), since circulation is controlled at the start.

Although laparoscopic cholecystectomy has replaced open cholecystectomy as the standard operation, there is still a place for the open approach (e.g. severe inflammation in the gallbladder and difficulties to identify anatomical structures). A right subcostal (Kocher) incision is widely used because it allows excellent exposure of the gallbladder bed and the cystic duct. An upper midline incision can be used if wider visibility to the other abdominal organs is needed. A right paramedian incision has also been used, but it is not common in current times.

The dissection of the gallbladder can be done by using two different methods: retrograde or anterograde techniques. The retrograde ("top down" or "fundus first") method dissection starts at the gallbladder fundus and proceeds towards the neck of the gallbladder. This technique is safe and facilitates sure identification of the cystic duct and artery. In anterograde techniques dissection begins at the triangle of Calot with dissection and ligation of the cystic artery and duct. After ligation, the gallbladder is dissected from the liver bed. (McAneny D 2008, Visser BC et al 2008)

2.6.2 Laparoscopic cholecystectomy

In 1983, a German gynaecologist, Kurt Semm (1983), performed the first endoscopic appendectomy. It inspired another German surgeon, Erich Mühe (1986, 1990, Litynski GS 1998), to develop the endoscopic surgical technique, and in 1985 he performed the first endoscopic cholecystectomy with a special "Galloscope".A French surgeon, Mouret (1996, Litynski GS 1999), continued to develope laparoscopic cholecystectomy and in 1987performed it in the same style as it is done today. Very rapidly after Mouret's discovery, laparoscopic cholecystectomy became popular without randomized trials, and in 1993 the National Institutes of Health made a consensus statement about laparoscopic cholecystectomy being the choice of treatment for most patients with symptomatic gallstones (Gollan J et al 1993).

The most common technique for laparoscopic cholecystectomy is a four trocar procedure. There are several alternatives in trocar placement. One common technique is where a camera-trocar is placed in the umbilicus and three trocars are placed in the right subcostal line. There are some studies which suggest that fewer trocars (two or three) might decrease the postoperative pain, but that the operation might be more difficult to perform. (Slim K et al 1995, Trichak S 2003, Poon CM et al 2003, Kumar M et al 2007)

Traditionally, the favoured method in laparoscopic cholecystectomy has been antegrade dissection, which means that the dissection of the gallbladder starts from the neck of the gallbladder. In difficult open cholecystectomy, a retrograde ("fundus first") dissection is often used to be sure about the cystic duct anatomy. If there are difficulties in identifying the

structures of Calot's triangle, a retrograde dissection can be used successfully also in laparoscopic cholecystectomy. The retrograde dissection might decrease the risk of conversion to the open cholecystectomy and common bile duct injuries. However, subtotal cholecystectomy or conversion must not be delayed if after the neck of the gallbladder is reached the anatomy is still unclear. (Martin IG et al 1995, Mahmud S et al 2002, Kelly MD 2009)

Obesity was a contraindication for laparoscopic cholecystectomy in the early years, but as early as in 1992 two studies indicated that obesity is not a contraindication, but rather an indication for laparoscopic cholecystectomy (Miles RH et al 1992, Schirmer BD et al 1992).

2.6.3 Single port laparoscopic cholecystectomy

Laparoscopic cholecystectomy is traditionally done with the four-trocar technique. Navarra G et al (1997) published the first series with 30 patients of single incision laparoscopic cholecystectomies. After 1997 several studies have been published where single incision laparoscopic cholecystectomy has been compared with conventional laparoscopic cholecystectomy. In a systematic review and meta-analysis Trastulli S et al (2013) analysed thirteen clinical trials covering a total of 923 procedures with single-incision versus conventional laparoscopic cholecystectomy. In their meta-analysis the conclusion was that single-incision laparoscopy has a higher procedure failure rate, more blood loss and takes longer than conventional multiport laparoscopic cholecystectomy.

2.6.4 Natural orifice transluminal endoscopic surgery

In 2004 Kalloo AN et al published an article about a transgastric peritoneoscopy in a porcine model, which was a start for skin incision-free laparoscopic surgery (natural orifice transluminal endoscopic surgery, NOTES).

The first NOTES cholecystectomy operation on a human being was performed in France in 2007 (Marescaux et al). The operation was done for a 30-year-old woman using a standard double-channel flexible gastroscope and standard endoscopic instruments through the vagina. However, only one 2 mm transabdominal needle port was used to insufflate carbon dioxide and to retract the gallbladder. Two years later de Sousa et al (2009) published the first series of pure NOTES transvaginal cholecystectomy. In four cholecystectomies they used two endoscopes through transvaginal incision.

In a systematic review Pollard JS et al (2012) analysed 714 NOTES and 3989 single-incision cholecystectomies. There were no differences in complications between the procedures, but NOTES took 30 minutes longer time (107 vs. 79 minutes). The NOTES cholecystectomy might be beneficial in terms of the cosmetic result, but otherwise the benefits of NOTES are far from clear.

2.6.5 Use of drainage

Traditionally drainage is often used in open cholecystectomy to prevent subhepatic abscess or bile peritonitis from an undrained bile leak. Cochrane systematic review (Gurusamy KS and Samraj K 2007) indicates that a drain increases harmswithout providing any additional benefit for patients undergoing open cholecystectomy in non-complicated gallstone disease and that it should thus be avoided. The effects of drains after elective laparoscopic cholecystectomy were

also evaluated. The conclusion was similar with the results of open surgery: the use of drains increases wound infection rates and delays hospital discharge without any benefit and should therefore be avoided.

2.6.6 Intraoperative cholangiography

Previously intraoperative cholangiography was considered an essential part of conventional open cholecystectomy. At that time ERCP was not available, and the recommendation was justifiable. (Pagana TJ et al 1980) Intraoperative cholangiography has been recommended to avoid CBD injury, but according to the latest reports cholecystectomy without routine intraoperative cholangiography is associated with a shorter operative time, fewer intraoperative complications and similar risk of CBD injury compared with routine intraoperative cholangiography (Sajid MS et al 2012).

Ford JA et al (2012) made a systematic review including eight randomised studies with 1715 patients. In that review they could not find robust evidence to support or abandon intraoperative cholangiography in cholecystectomy.

2.6.7 Ultrasonic dissection in cholecystectomy

Monopolar electrosurgical energy is the most frequently used energy form in order to achieve adequate dissection and haemostasis in minilaparotomy and in laparoscopic cholecystectomy. Monopolar electrosurgical energy has been used routinely because of low cost and easy usability for securing haemostasis. It is unselective for cutting fibrous tissue, however, which can increase the danger of biliary complications and thermal injuries (Gossot D et al 1999). In 1995, Amaral JF introduced ultrasonic dissection in laparoscopic cholecystectomy as a safe and effective instrument. In Amaral's study 200 consecutive laparoscopic cholecystectomies were performed without any major complications.

Sietses C et al (2001) compared the postoperative systemic immune response after monopolar electrosurgery and ultrasonic surgery in laparoscopic cholecystectomy. In a small randomised series of 18 patients there were no differences between the study groups.

Since then the use of ultrasonic dissection in laparoscopic cholecystectomy has been evaluated in several studies (Janssen IM et al 2003, Cengiz Y et al 2005, Bessa SS et al 2008, Cengiz Y et al 2009, El Nakeeb A et al 2010, Kandil T et al 2010, Redwan AA 2010, Jain SK 2011). The results indicate that ultrasonic dissection leads to a shorter recovery time (El Nakeeb A et al 2010, Kandil T et al 2010, Jain SK et al 2011) and fewer postoperative complications in laparoscopic cholecystectomy than the monopolar electrosurgical energy technique (Janssen IM et al 2003, Bessa SS et al 2008, El Nakeeb A et al 2010, Kandil T et al 2010, Cengiz Y et al 2009, Jain SK et al 2011).

To the best of our knowledge, the use of ultrasonic dissection in minilaparotomy cholecystectomy has not been evaluated.

2.6.8 Minilaparotomy cholecystectomy

2.6.8.1 Definition of minilaparotomy

There are no international criteria for minilaparotomy. One of the first series of small incision cholecystectomy was published by Ledet WP (1990), who performed minilaparotomy cholecystectomy on 200 consecutive patients (age range 16-82 years) whose only selection criterion was that they wanted the surgery to be a day case. All patients were discharged three to 10 hours postoperatively and subsequently experienced no significant complications. At the same time with the Ledet report, O'Dwyer PJ et al (1990) published an article where they described cholecystectomy through a 5 cm long incision. Al-Tameem MM (1993) consecutively performed 80 minilaparotomy cholecystectomies with a 3-5 cm incision. Altogether 90% of the patients were discharged within two days and returned to work within 10 days.

Is minilaparotomy only a short incision? O'Dwyer PJ et al (1992) randomised 30 patients to 6 cm or 15 cm transverse subcostal incision cholecystectomy groups. In the short incision group the hospital stay was 2 days shorter compared to the long incision group. Tyagi NS et al (1994) described a new minimal invasive microceliotomy technique, where there was a 3 cm long transverse high subxiphoid incision in the so called "minimal stress triangle" and the rectus muscle was not cut but instead it was retracted laterally. In this study with 143 patients the day-case procedure was successful in 73% of the patients.

Schmitz R et al (1997) randomised 130 patients in two groups, 65 patients to subcostal short incision group (mean length 6 cm) and 65 patients to conventional cholecystectomy trough paracostal incision of mean length 13 cm. Surprisingly they could not find marked difference between the groups for pain and consumption of analgesics.

Seale AK and Ledet WP Jr (1999) had good results with minicholecystectomy where they made a 4-7 cm long transverse incision 2 to 3 fingers below the xiphoid process, and preserved as much of the rectus muscle as possible. In their study 1207 patients underwent minicholecystectomy. 74% of the patients were admitted for day surgery and 88% of them were discharged in less than 12 hours.

2.6.8.2 Minilaparotomy cholecystectomy in randomised studies

Randomised studies (published in English) with minilaparotomy cholecystectomy vs. laparoscopic cholecystectomy are shown in table 1. The first randomised trial between minilaparotomy and laparoscopic cholecystectomy was carried out by Barkun JS et al (1992). In their study 70 patients with symptomatic gallstones were randomised to a minilaparotomy or a laparoscopic cholecystectomy group. The laparoscopic procedure was better than minilaparotomy in terms of the mean hospital stay, the duration of convalescence and the return to normal daily activities.

McMahon AJ et al (1993) conducted a small randomised study, where they compared laparoscopic cholecystectomy (n=10) and minilaparotomy cholecystectomy with a 5-7-cm incision (n=10). They studied metabolic responses after minilaparotomy and laparoscopic cholecystectomy. There were several metabolic changes from baseline, but no significant difference between the two groups.

The following year McMahon AJ et al (1994) published a trial of 302 patients randomised to a laparoscopic or a minilaparotomy group. In that study minilaparotomy was faster and less costly, but postoperative recovery was better in the laparoscopic group, when the length of the hospital stay, the return to work and daily activities were evaluated. After one year the patients were followed up with a questionnaire and the only difference between the treatment groups was that heart burn was reported twice as often by the minilaparotomy group compared to the laparoscopic group: 35% vs. 19% respectively (McMahon AJ 1995). McMahon AJ et al (1994) published another study, where they compared postoperative pulmonary function and pain between minilaparotomy (n=65) and laparoscopic cholecystectomy (n=67). Patients in the laparoscopic group had less pain, the consumption of morphine was half of that in the minilaparotomy group, and their postoperative pulmonary function and oxygen saturation were better than among patients in the minilaparotomy group.

McGinn FP et al (1995) analysed 310 randomised cholecystectomies divided into minilaparotomy and laparoscopic cholecystectomy groups. The conversion rate in the laparoscopic group was rather high, 13% versus 4% in the minilaparotomy group. If laparoscopy was successful, the hospital stay was significantly shorter in the laparoscopic group than in the minilaparotomy group, but overall the hospital stay was not significantly different. The return to normal activities and to work was faster after laparoscopy than after minilaparotomy. In terms of costs there were no differences between the two procedures.

The first Finnish results about minilaparotomy cholecystectomy were published by Mäkinen AM and Nordback IH (1995). In their study, there were eight patients in the minilaparotomy group and 16 in the laparoscopic group. The study was stopped after the pilot phase, since the outcomes after minilaparotomy cholecystectomy were so much poorer, and the method was therefore abandoned.

Majeed AW et al (1996) randomised 200 patients into minilaparotomy and laparoscopic cholecystectomy groups. Minilaparotomy cholecystectomy was faster than laparoscopic cholecystectomy. In contrast to McMahon (1993), the laparoscopic procedure had no advantages in terms of hospital stay or postoperative recovery.

In a Swedish single-blind, multicenter trial (Ros A et al 2001) altogether 724 patients were randomised to minilaparotomy and laparoscopic group. Minilaparotomy was defined as less than an 8 cm long transverse subxiphoid or a short oblique incision and muscle splitting was allowed when considered necessary. Minilaparotomy was faster than laparoscopic cholecystectomy (median operating time 85 vs. 100 min). The median hospital stay was two days in both groups, but in a nonparametric statistical analysis the hospital stay was significantly shorter after the laparoscopic procedure. The median sick leave was three days shorter (13 vs. 16 days) in the laparoscopic group than in the minilaparotomy group, and the return to normal daily activities 2 days shorter (9 vs. 11 days). In terms of complications there were no differences between the groups.

The one-year follow-up results of the Swedish study on minilaparotomy vs. laparoscopic cholecystectomy were published in 2004 (Ros A and Nilsson E 2004). There were no differences between laparoscopic and minilaparotomy cholecystectomy in terms of the long-term outcomes, but residual abdominal pain was common in both groups. Also the quality of life and costs were analysed by the same study group (Nilsson E et al 2004). The total costs were similar between minilaparotomy and laparoscopic cholecystectomy with high volume surgery, but laparoscopic cholecystectomy was more expensive with fewer operations and disposable trocars. The health-related quality of life was slightly better in the laparoscopic group one week after the surgery, but one month and one year postoperatively there were no differences between the groups.

In earlier cost-effectiveness analyses laparoscopic cholecystectomy has been more costly, but in an Indian study (Srivastava A et al 2001) laparoscopic cholecystectomy seemed to be more cost-effective than minilaparotomy cholecystectomy. In their study minilaparotomy was done by a transverse rectus cutting incision and minilaparotomy was successful only in 15 patients out of 40.

Oyogoa SO et al (2003) compared minilaparotomy and laparoscopic cholecystectomy patients in a two-year retrospective review. In that single surgeon study 66 patients were matched for age, body surface area and Acute Physiology and Chronic Health Evaluation II (APACHE II) score for two groups. In the study the absolute cost was lower for the minilaparotomy group than for the laparoscopic cholecystectomy group, and there were no differences in terms of postoperative recovery between the groups.

Syrakos T et al (2004) analysed retrospectively altogether 1 276 cholecystectomy patients covering a six year period. Laparoscopy was used in 952 patients, conventional open cholecystectomy in 210 patients and minilaparotomy cholecystectomy in 114 patients. In the conventional cholecystectomy group the hospital stay was 2 days longer than in the minilaparotomy or laparoscopic group. The median operating time was shorter in the minilaparotomy group than in the laparoscopic group (46 vs. 61 min), and minilaparotomy was 200 Euros less costly for the hospital than laparoscopy.

Vagenas K et al (2006) randomised 88 patients to laparoscopic or minilaparotomy cholecystectomy. Minilaparotomy was done through the rectus abdominis muscle through a small incision. The laparoscopic procedure lasted longer than minilaparotomy, but the patients stayed a shorter time at the hospital. After laparoscopy the patients used less opioids in the postoperative period and the time it took to resume to normal activity was shorter than in the minilaparotomy group. In addition, the aesthetic results were better after the laparoscopic operation.

Purkayastha S et al (2007) used meta-analytic techniques to compare the perioperative and short-term post-operative outcomes for patients operated with laparoscopy or minilaparotomy. They analysed all randomised control trials published between 1992 and 2005. Altogether 9 randomised control trials including 2032 patients were accepted in the meta-analysis. The conclusion in the meta-analysis was that there are not great differences between laparoscopic or minilaparotomy cholecystectomy, but minilaparotomy is faster in operating time and the length of the hospital stay is slightly reduced after the laparoscopic procedure.

Rosenmüller MH et al (2013) made an expertise-based randomisation between laparoscopic and minilaparotomy cholecystectomy including 333 patients. The patients were randomised to treatment by one of two teams of surgeons with preference for either laparoscopy or

minilaparotomy. Laparoscopy was slightly better when the postoperative quality of life was measured, but there were no significant differences between the two groups in terms of pain, conversion rate, complications, and the length of the hospital stay or readmissions.

In the Cochrane Database Systematic Review Keus F et al (2010) analysed three different techniques of cholecystectomy: open, minilaparotomy, or laparoscopic. Altogether 56 randomised studies with 5246 patients were analysed. The recovery after minilaparotomy cholecystectomy and laparoscopic cholecystectomy was better than after open conventional cholecystectomy. There was no significant difference between minilaparotomy and the laparoscopic procedures in recovery time, but the operative time was shorter in the minilaparotomy method and it seemed to be less costly.

Table 1. Randomised trials of minilaparotomy vs. laparoscopic cholecystectomy (published in English) LC=laparoscopic cholecystectomy, MC=minilaparotomy cholecystectomy.

Author and year	Country of origin	Number of patients	Outcome
Barkun JS 1992	Canada	30+32	LC, shorter hospital stay
McMahon AJ 1993	United Kingdom	10+10	No significant difference
McMahon AJ 1994	United Kingdom	150+152	MC, less costly
McMahon AJ1994	United Kingdom	67+65	LC, less pain
McGinn FP 1995	United Kingdom	155+155	LC, faster convalescence
Mäkinen AM 1995	Finland	8+16	MC abandoned in pilot phase
Majeed AW 1996	United Kingdom	100+100	MC, faster operation
Ros A 2001	Sweden	362+362	LC, faster convalescence
Srivastava A 2001	India	59+41	LC, less costly
Vagenas K 2006	Greece	44+44	LC, faster convalescence
Rosenmüller MH 2013	Sweden	177+156	LC, better quality of life

3 *Aims of the Study*

Laparoscopic cholecystectomy is regarded as the gold standard of intervention for gallstone disease. However, laparoscopic procedures need special equipment, and there is a learning curve when laparoscopic procedures are learned. Thus, it was hypothesised that an advanced open technique, minilaparotomy, could be a feasible option.

The recent study was undertaken to evaluate the safety and efficacy of minilaparotomy cholecystectomy compared with laparoscopic cholecystectomy. More specifically, the aims of this study were:

1. To compare perioperative and short-term parameters, outcome and morbidity between minilaparotomy and laparoscopic cholecystectomy (I, IV, VI).
2. To evaluate the quality of life after minilaparotomy and laparoscopic cholecystectomy (II).
3. To evaluate the feasibility of minilaparotomy cholecystectomy for day surgery (III, IV).
4. To evaluate the long-term outcome after minilaparotomy and laparoscopic cholecystectomy (V).
5. To evaluate the usefulness of ultrasound scissors in minilaparotomy cholecystectomy compared to standard laparoscopic cholecystectomy (VI).

4 Patients and Methods

The total number of patients in this study was 335 (188 in the minilaparotomy groups and 147 in the laparoscopic groups).The major characteristics of the subjects are presented in Table 2.

Table 2. Demographic characteristics of the patients in the studies I-VI. Data is number of cases, median, (minimum-maximum).

Study	**Number of patients**	**Gender male/female**	**Age**	**BMI**
Study I, II, V	MC: n=85 LC: n=72	20/65 12/60	49 (17-78) 50 (17-76)	27 (18-48) 26 (19-36)
Study III	MC: n=30	4/26	55 (27-68)	30 (19-41)
Study IV	MC: n=29 LC: n=31	5/24 7/24	46 (21-63) 42 (18-66)	27 (21-47) 26 (18-35)
Study VI	MC: n=44 LC: n=44	8/36 3/41	44 (21-73) 44 (19-64)	24 (18-35) 26 (17-35)

- BMI= body max index (kg/m^2); MC=minilaparotomy cholecystectomy; LC=laparoscopic cholecystectomy

4.1 PATIENTS AND STUDY DESIGN

The studies were carried out at the Department of Surgery, Kuopio University Hospital, Kuopio, Finland; at the Kuusankoski District Hospital, Kuusankoski, Finland; at the Department of Surgery, Päijät-Häme Central Hospital, Lahti, Finland; and at the Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland in the years 1998 – 2012. The study was approved by the Research Ethics Committee of Hospital District of Northern Savo,

Kuopio, Finland (study I-VI); the Joint Ethics Committee of the Hospital District of Kymenlaakso, Kuusankoski and Kotka, Finland (study IV) and the Ethics Committee of Helsinki and Uusimaa University District, Helsinki, Finland. It was registered in the ClinicalTrials.gov database (ClinicalTrials.gov Identifier: NCT0172340) (study VI) and it was concluded in accordance with the Declaration of Helsinki. The participants gave written consent after receiving verbal and written information.

Elective patients with symptomatic gallstones confirmed by ultrasound and suitable for surgery were included in the study. The exclusion criteria specified earlier jaundice, suspicion of stones in the common bile duct (serum elevated alkaline phosphate or bilirubin or a wide common bile duct on ultrasound), previous upper abdominal operation (relative exclusion criteria), and cirrhosis of the liver or suspicion of cancer.

Studies I, II, IV, V and VI were prospective, randomised and open in design and study III was a prospective pilot study on minilaparotomy patients. Randomisation was computer-generated and concealed before enrolment using a sealed envelope method. Altogether 157 patients were randomised to either minilaparotomy cholecystectomy (n=85) or laparoscopic cholecystectomy (n=72) groups between February 1998 and April 2004 in studies I, II and V in which the operations were carried out at the Kuopio University Hospital. A flow chart of studies I, II and V is shown in Figure 1.

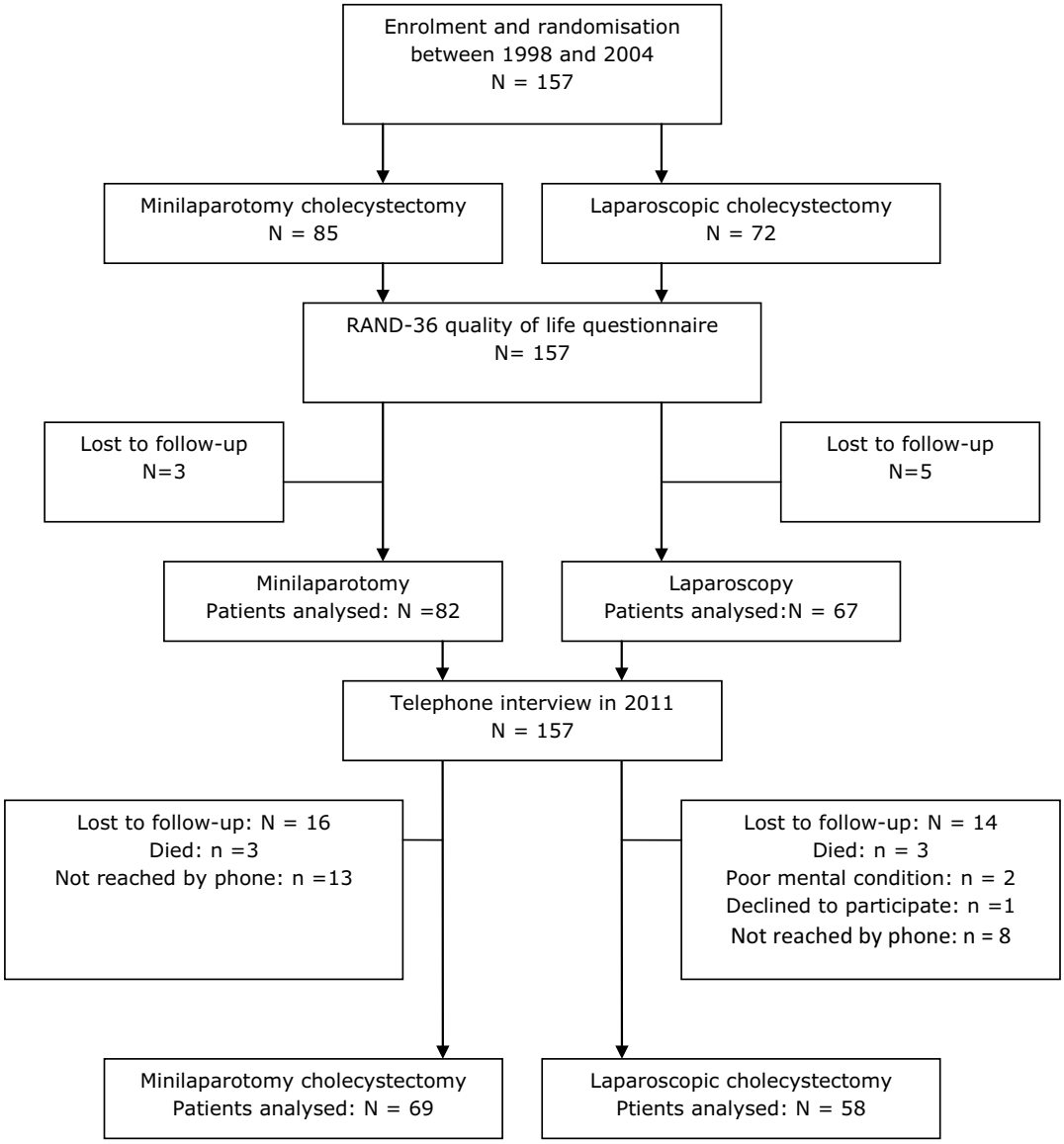


Figure 1. Flow chart of studies I, II and V.

In study III 30 elective symptomatic patients without complications were included between the end of the year 2004 and June 2005 and operations were performed at the Kuopio University Hospital. In study IV the operations (n=60) were carried out in the Department of Surgery at the Kuusankoski District Hospital (n=38) and at the Kuopio University Hospital (n=22) between February 2006 and April 2008 with 29 patients in the minilaparotomy group and 31 in the laparoscopic group. In study VI the operations were carried out in three hospitals in Finland; Helsinki University Central Hospital, Helsinki (n=24), Kuopio University Hospital, Kuopio

(n=34) and Päijät-Häme Central Hospital, Lahti (n=30) between September 2010 and April 2012. All operations were performed with similar endotracheal anaesthesia in all the hospitals and across the studies.

Altogether 18 surgeons were involved. In study I (in studies II and V the material was the same) 18 operators performed operations, 11 of whom were trainees and 7 consultants. In the pilot study III one consultant surgeon performed all operations. In study IV three consultant surgeons performed all operations and in study VI there were four consultant surgeons. In the minilaparotomy group a basic operating basket also containing two short and two long Langenbeck hooks and triangle forceps was used. The surgeon used a head lamp in the minilaparotomy operations. The placement of trocars in laparoscopy and the site of the minilaparotomy incision are shown in figure 2. The minilaparotomy cholecystectomy technique is illustrated in figure 3.

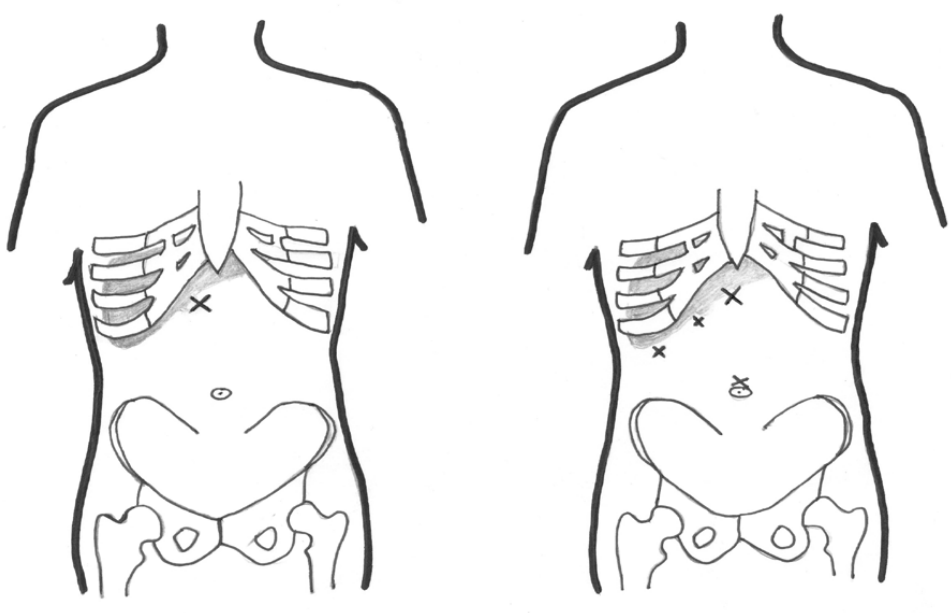


Figure 2. Placement of transverse incisions are marked with an **X**. Minilaparotomy on the left and laparoscopy on the right.

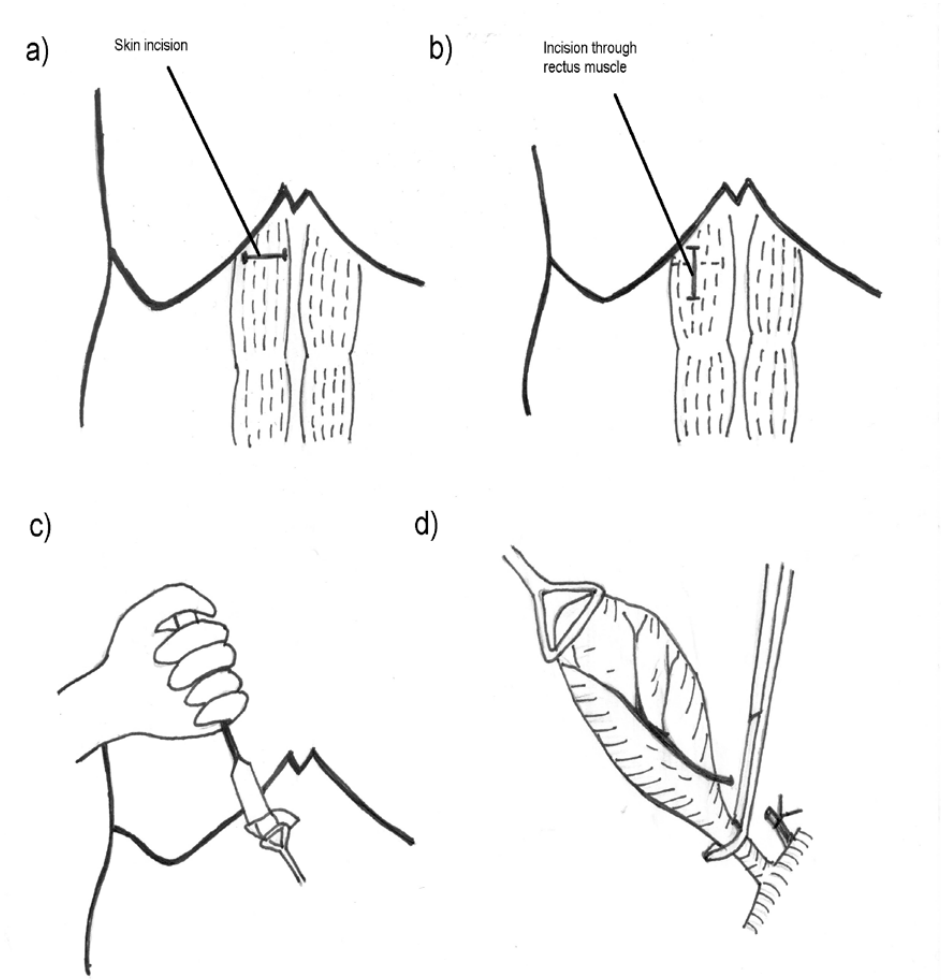


Figure 3. a) Placement of horizontal skin incision. b) Longitudinal incision through rectus muscle. c) The operation is assisted with a Langenbeck hook. The gallbladder is held with a triangle forceps. d) The artery is ligated or sealed with ultrasonic dissection, and the cystic duct is ligated with an absorbable ligament or with an absorbable clip.

4.2 PAIN MEASUREMENTING (I–VI)

Pain was assessed in the patients using a visual analogue scale (VAS) or with an 11-point numeric rating scale (NRS) (0=no pain; 10= most pain). The measuring of pain was performed by asking the patient about the pain in the recovery room and in the ward, or in the day surgery ward at one hour intervals upto eight hours postoperatively and on the first postoperative day by phone or in person if the patient was still in the ward. Four weeks postoperatively patients returned a questionnaire where the pain was evaluated by NRS.

4.3 POSTOPERATIVE PULMONARY FUNCTION (I)

Pulmonary function (forced vital capacity [FVC], forced expiratory volume in 1 s [FEV_1] and peak expiratory flow rate [PEFR]) were measured postoperatively and on the first postoperative day. Measurements were made by portable spirometry (Escort, Buckingham, England).

4.4 QUALITY OF LIFE (II, V)

In study II the quality of life was measured with RAND-36 quality of life questionnaire (Hays RD and Morales LS 2001) four weeks after the surgery at a follow-up visit or else the patients returned the questionnaire. The RAND-36 quality of life questionnaire was successfully completed by 67 (93%) out of 72 patients in the laparoscopic group and 82 (96%) out of 85 in the minilaparotomy group. For those who did not come to the follow-up visit the questionnaire was posted to be returned in a prepaid envelope. In study V the quality of life was evaluated with a 5-point Likert-scale (much better, better, could not say, worse, much worse). The interview in study V was made by phone.

4.4 LONG-TERM FOLLOW-UP (V)

In study V patients, operated in study I, were interviewed by telephone between August and October 2011. The interviewer had not participated in the treatment of the study patients and was blinded to the operation technique used in cholecystectomy. The flow chart of study V is included in Figure 1. In both of the groups 81% of the original patients were interviewed for the study. In the study a 5-point Likert-scale with structured questions was used. The questions were related to postoperative food intolerance, pain, the quality of life and the satisfaction in the operation.

4.5 STATISTICAL METHODS (I–VI)

The data was entered and analysed with a statistical software program (IBM SPSS Statistics 19, IBM, Somers, USA). The results are presented as mean and standard deviation, median and minimum and maximum, or as the number of patients when appropriate. In the statistical analyses, the Mann-Whitney *U*-test and repeated measures analysis of variance (ANOVA) were used. If the data was normally distributed, the independent samples t -test was used to compare the ordinal and continuous data. The Pearson chi-square test was used to analyse the differences for the frequency data. A two-sided p-value of less than 0.05 was considered statistically significant.

5 Results

5.1 PERIOPERATIVE OUTCOME (I, III, IV, VI)

In study I minilaparotomy cholecystectomy was statistically a significantly faster operation to perform than laparoscopic cholecystectomy. The overall time at the operating theatre was significantly shorter in the minilaparotomy group also. Such difference between the two procedures was not found in studies IV and VI (Table 3).

Table 3. Perioperative outcomes. Data is mean (standard deviation) and median [range].

Study (years)	**Operative time** (minutes)	**Overall time in the operating theatre** (minutes)	**Conversion rate**
Study I* (1998-2004) MC n=85 LC n=72	MC: 55 (19) 50 [20-125] LC: 79 (27) 75 [35-170]	MC: 102 (22) 97 [65-161] LC: 127 (32) 125 [75-228]	MC: 2/85 (2%) LC: 4/72 (6%)
Study III (2004-2005) MC n=30	MC: 51 (16) 50 [30-105]	MC: 86 (17) 84 [65–140]	MC: 4/30 (13 %)
Study IV (2006-2008) MC n=29 LC n=31	MC: 62 (14) 61 [38–105] LC: 61 (27) 56 [29–137]	MC: 115 (15) 120 [90–150] LC: 118 (25) 118 [69–180]	MC: 1/29 (3%), LC: 3/31 (10%)
Study VI (2010-2012) MC n=44 LC n=44	MC: 55 (14) 54 [28–104] LC: 57 (25) 60 [25–167]	MC: 107 (16) 108 [70–140] LC: 113 (22) 110 [74–213]	MC: 1/44 (2%) LC: 2/44 (5%)

*p<0.001 (Mann-Whitney U-test) for the operative time and for overall time in the operating theatre.

MC=minilaparotomy cholecystectomy; LC=laparoscopic cholecystectomy

There was not a statistically significant difference in the conversion rate to conventional cholecystectomy between minilaparotomy and laparoscopic cholecystectomy (studies I, IV, VI).

The numbers of conversions in the minilaparotomy groups were 8/188 (4%) and in the laparoscopy groups 9/147 (6%).

5.2 EARLY RECOVERY AFTER SURGERY (I, III, IV, VI)

In study I the mean hospital stay was longer than in studies III, IV and VI, but study I was not planned as a day surgery basis. There was small variation in the mean length of the sick leave between the different studies (from 13 to 17 days), but only in study VI there was a significant difference between the two groups. In study VI the mean sick leave was three days shorter in the minilaparotomy group than in the laparoscopic group. (Table 4)

Table 4. Short-term outcomes. Data is mean, (standard deviation) and median [range].

Study	**Hospital stay (days)**	**Sick leave mean (days)**	**Complications**	**Readmissions**
Study I MC n=85 LC n=72	MC: 2.1 (1) 2 [1-7] LC: 2.1 (2) 2 [1-20]	MC: 17 (5) 15 [8-38] LC: 16 (4) 14 [8-38]	MC: 3/85 4% LC: 1/72 1%	not recorded
Study III MC n=30	MC: 0.2 (1) 0 [0-1]	MC: 16 (5) 14 [14-30]	MC: 1/30 3%	MC: 1/30 3%
Study IV MC n=29 LC n=31	MC: 0.3 (1) 0 [0-1] LC: 0.6 (1) 0 [0-5]	MC: 16 (3) 14 [12-28] LC: 18 (6) 14 [12-28]	MC: 2/29 7% LC: 2/31 7%	LC: 1/31 3%
Study VI* MC n=44 LC n=44	MC: 0.1 (0.3) 0 [0-1] LC: 0.2 (0.4) 0 [0-1]	MC: 13 (3) 14 [1-21] LC: 16 (5) 14 [8-34]	MC: 2/44 5% LC: 2/44 5%	MC: 2/44 5% LC 2/44 5%

*p=0.01 for sick leave (Mann-Whitney U-test).

MC=minilaparotomy cholecystectomy; LC=laparoscopic cholecystectomy

In terms of complications there was no difference between the minilaparotomy and the laparoscopic cholecystectomy groups. In the randomised studies (I, IV and VI) the total number of complications was 7/158 (4%) among the minilaparotomy groups and 5/147 (3%) among the

laparoscopic groups. In study I the readmissions were not calculated, but in studies IV and VI there were no statistically significant differences in the readmissions rates between the minilaparotomy and laparoscopic groups.

In study I the postoperatively pulmonary function was decreased in both groups, but there was no difference between the minilaparotomy and laparoscopic groups. The mean forced vital capacity was preoperatively 3.4 litres in both groups and postoperatively 2.8 litres in the laparoscopic group and 2.7 litres in the minilaparotomy group.

In the randomised studies (I, IV and VI) there were no statistically significant differences between the groups in terms of postoperative nausea and vomiting. Postoperative pain and use of analgesics did not differ between the groups in studies I and IV, but in study VI there was significantly less postoperative pain on the operation day in the minilaparotomy group (Table 5) and the total use of analgesics after surgery was three days shorter compared to the laparoscopic group (7 days range 2-19 vs. 10 days range 2-40, p= 0.024).

Table 5. Postoperative pain in the two study groups in study VI. Pain was assessed with an 11-point numeric rating scale (0 = no pain, 10 = most pain). Data is mean (standard deviation) and median [range].

Pain at hospital	**Minilaparotomy cholecystectomy n=44**	**Laparoscopic cholecystectomy n=44**	**p-value** (Mann-Whitney U-test)
At 1 hour	2.8 (1.8) 2 [0-7]	4.0 (2.6) 4 [0-9]	0.028
At 2 hours	1.6 (1.5) 1 [0-6]	3.0 (2.7) 2 [0-10]	0.011
At 3 hours	1.3 (1.7) 1 [0-7]	2.5 (2.0) 2 [0-8]	0.001
At 4 hours	1.3 (1.2) 1 [0-4]	2.1 (1.9) 2 [0-7]	0.05

5.3 SUITABILITY FOR DAY SURGERY (III, IV, VI)

In study III, 25 patients out of 30 (83%) were discharged at the operation day. Five patients were discharged on the first postoperative day. Conversion to conventional cholecystectomy was the reason for staying overnight in four cases and wound pain and vomiting in one case. In study IV the day surgery success rate was 19 out of 29 patients in the MC-group and 17 out of 31 patients in the LC-group without statistically significant difference between the groups. In study VI the success of day surgery in the minilaparotomy group was 87% (39/44) and in the laparoscopic group 82% (36/44) (p=0.37). There were three conversions in study VI, but all of them were discharged on the operative day.

5.4 PATIENT DEPENDENT EARLY RECOVERY (I, III, IV)

In study I obesity was specially observed. There was no statistically significant difference between obese (BMI >30 kg/m^2) and non-obese patients when the operating time and the time at the operating theatre were compared. Surprisingly, the operating time among the obese minilaparotomy group was a quarter of an hour shorter than that among the non-obese laparoscopic group (65 min [37-125] vs. 78 min [35-170]).

On the contrary, in study III the operative time was a quarter of an hour longer among the obese patients (46 min [30–77]) than that among the non-obese patients (59 min [40–105] p= 0.013). All conversions in study III were done for obese patients.

In study IV chronic inflammation (a thick wall gallbladder and chronic inflammation on histology) seemed to have had a significant effect on the success of day surgery. If there was chronic inflammation in the gallbladder, day surgery was successful in only 41% of the cases (9/22), but if not, same day discharge was possible in 75% of the cases (26/38, p=0.023), respectively.

5.5 QUALITY OF LIFE (II, V)

In study II, patients whose BMI was <30 kg/m^2 had better postoperative physical functioning (p=0.01), but obesity did not have any significant effect on other RAND-36 variables. The role functioning/physical score (63 vs. 49, p=0.038) was slightly better in the laparoscopic group, but in other RAND-36 variables there were no statistically significant differences between the two groups.

In study V, where the quality of life was investigated with a 5-point Likert-scale, 90% (67/69) of the patients in the minilaparotomy group felt that their quality of life had improved compared to the time before the operation, whereas the rest of patients had had no change in the quality of life. In the laparoscopic group 95% (55/58) of the patients had a better quality of life after the operation. One patient in the laparoscopic group felt that their quality of life was worse postoperatively.

5.6 LONG-TERM OUTCOME (V)

Residual abdominal symptoms were common in both groups, but there was more residual abdominal pain in the laparoscopic group. In the minilaparotomy group 5 patients out of 64 and in the laparoscopic group one patient out of 57 had chronic post-surgical pain, but the difference was not statistically significant. Dietary intolerance for fatty and fried food was common in both groups, but about half of the patients felt fewer reflux symptoms after the operation.

Altogether 95% of the patients in both groups were satisfied in the operation and the cosmetic result and were ready to recommend the operation for others. There was no statistically significant difference between the two groups.

6 Discussion

6.1 REVIEW OF STUDY SAMPLE SIZE AND DESIGN

6.1.1 Study sample size

In study I (II and V) the total number of patients was 157 (85 in the minilaparotomy group and 72 in the laparoscopic group), which might be considered adequate compared with other studies (Purkayastha S et al 2007). In the follow-up study (V) the response rate was high (over 80% of the patients in both groups were reached), which can be considered a good result. Study III was a pilot study, without comparison with other groups, and 30 patients can be considered sufficient to show if the procedure may be applicable to day surgery. The study size in study IV was estimated according to study III. It might be considered too small, but obvious differences between the two groups should have been shown with this sample size. In study VI the sample size calculation was based on the assumption that the convalescence should be 16 days (SD 4) in the laparoscopic group (study I). In order to show a 3-day difference in the convalescence between the two groups, 40 patients per group were required at a study power of 0.9 and two-sided α-level of 0.05 to show a statistically significant difference between the groups. Therefore the sample size of 88 patients should be sufficient.

6.1.2 Study design and perspective

Laparoscopic cholecystectomy is the gold standard for operative treatment of gallstone disease to which all other invasive treatments should be compared. When the study was started there were only a few studies about minilaparotomy without comparison to laparoscopy (Ledet WP 1990, O'Dwyer PJ et al 1990, Al-Tameem MM 1993, Tyagi NS et al 1994) and only few randomised series (Barkun JS et al 1992, McMahon AJ et al 1993, McMahon AJ et al 1994, McGinn FP et al 1995, Mäkinen AM et Nordback IH 1995, Majeed AW et al 1996) with contradictory results. Since the results from these studies were not consistent, study I was planned in order to clarify whether there is a difference between minilaparotomy and laparoscopic cholecystectomy. Before the study was started there was the possibility that obesity might cause difficulties to perform minilaparotomy and hence no limits in the patients' BMI were set to show what influence obesity might have, if any. In every new procedure there is a learning curve. Minilaparotomy was a new method for all surgeons in the hospital at the time the study was started, but everybody had experience in conventional open cholecystectomy. A total of 18 surgeons performed the operations. Trainees (n=11) were also included among the operating surgeons in order to show whether the learning curve affected the study variables.

The RAND-36 quality of life questionnaire was used to evaluate the outcome. This questionnaire is established in Finnish studies, and is also used internationally (Aalto A-M et al 1999).

At the time the first study was planned, day surgery was not a common protocol for cholecystectomy. Therefore the first study was made on an in-hospital surgery basis. When

study III was designed there were not much published data about minilaparotomy cholecystectomy (Ledet 1990, Saltzstein EC et al 1992, Seale AK and Ledet WP Jr 1999, Thomas S et al 2001). Hence the study was a pilot protocol to evaluate whether minilaparotomy is feasible for day surgery.

Because day surgery was successful with most patients in study III, study IV was designed to prospectively compare minilaparotomy and laparoscopic cholecystectomy performed as day surgery.

Study V was carried out as a telephone interview. A telephone interview was chosen, because most people have telephones (Tilastokeskus 2012), and it was thought that patients would find it easier to participate in a telephone interview rather than answer posted forms or visit the surgery outpatient. In order to ensure the independence of the interview, the interviewer was a person who had not participated in the operations.

As far as it was known, there were no previous studies where ultrasonic dissection had been used in minilaparotomy cholecystectomy. When study VI was planned, originally four interventions were planned: minilaparotomy with monopolar electrosurgical energy, minilaparotomy with ultrasonic dissection, laparoscopy with monopolar electrosurgical energy, and laparoscopy with ultrasonic dissection. A very large number of patients would have been required in order to include four different surgical techniques in a single study. Because laparoscopic cholecystectomy is nowadays a standard treatment and in earlier studies there have not been significant differences between conventional laparoscopy and conventional minilaparotomy, it was decided to compare ultrasonic dissection minilaparotomy with conventional laparoscopy.

6.2 PERIOPERATIVE AND SHORT-TERM OUTCOMES (I, III, IV, VI)

In some of the earlier studies without randomisation to minilaparotomy and laparoscopy (Ledet WP 1990, O'Dwyer PJ et al 1990, Al-Tameem MM 1993, Tyagi NS et al 1994) there were encouraging results of minilaparotomy cholecystectomy.

In the first randomised studies laparoscopic cholecystectomy seemed to be better than minilaparotomy cholecystectomy when short-term recovery was measured (Barkun JS et al 1992, McMahon AJ et al1994, McGinn FP et al 1995, Mäkinen AM and Nordback IH 1995). In 1996 Majeed AW et al had similar results between minilaparotomy and laparoscopic cholecystectomy in hospital stay and postoperative recovery, and minilaparotomy was the faster procedure.

During the last fifteen years, there have been contradictory results in different studies, where laparoscopic and minilaparotomy cholecystectomies have been compared. In some studies there have not been significant differences between minilaparotomy and laparoscopic cholecystectomy (Oyogoa SO et al 2003, Syrakos T et al 2004, and Velázquez-Mendoza JD et al 2012). On the other hand, the laparoscopic procedure has had some advantages in other studies (Srivastava A et al 2001, Vagenas K et al 2006)

The results in the present study indicate that minilaparotomy cholecystectomy is as good as laparoscopic cholecystectomy when postoperative outcome is considered. The overall time at the operating theatre was shorter in the minilaparotomy group than in the laparoscopic group in study I, but the clinical relevance of a 25-minute difference is minimal in clinical practice,

since there was much variation in the overall time within both groups. Furthermore, such a difference between the groups was not found in studies IV and VI. Laparoscopic cholecystectomy was a rather new method at the time when study I was started, which might explain the longer operating time in the laparoscopic group.

In short-term results there were no differences between the two groups in hospital stay, complications or readmissions. However, in study VI sick leave was three days shorter in the minilaparotomy group than in the laparoscopic group. Postoperative pain and the use of analgesics in the operations were similar in studies I and IV, but in study VI there was less postoperative pain in the minilaparotomy group and also the total use of postoperative analgesics was three days shorter than in the laparoscopic group. Better recovery in the minilaparotomy group in study VI might suggest that ultrasonic dissection really benefits recovery. Reason for that might be a lesser tissue damage in ultrasonic dissection technique.

In study I, there was no difference between the groups in terms of postoperative pulmonary function. McMahon AJ et al (1994) found better postoperative pulmonary function after laparoscopic cholecystectomy than after minilaparotomy. This contradictory result may reflect the difference in the minilaparotomy incision technique in the present study compared to McMahon's technique.

6.3 PATIENT DEPENDENT RECOVERY (I, III, IV)

In the present study it was hypothesised that obesity might cause problems, especially in minilaparotomy. In study I, no significant difference between obese (BMI > 30kg/m^2) and non-obese patients were identified. The mean operating time was even shorter in the obese minilaparotomy group than in the non-obese laparoscopic group. In study III the result was contradictory to study I. All conversions were done for obese patients in study III, and therefore the mean operating time was longer. This indicates that obesity increases difficulties in the minilaparotomy operation. In study I, it is possible that laparoscopic skills were not as developed for all surgeons as in later studies and number of surgeons was much bigger in study I than in later studies. Also laparoscopic instrumentation, especially cameras and monitors, have developed rapidly during last decade, which might have influenced operating time.

In study IV chronic inflammation in the gallbladder had a significant effect on operations in both groups. The mean operating time was longer, and even if laparoscopy or minilaparotomy was successful, same-day discharge was much less often possible for patients with chronic inflammation than those without. If there is a clinical suspicion of chronic inflammation before cholecystectomy (a thick wall gallbladder in the ultrasound, previous cholecystitis), day surgery is probably not the best option, or at least patients should be informed about the risk for overnight admission.

6.4 QUALITY OF LIFE AFTER CHOLECYSTECTOMY (II, V)

To the best of our knowledge, the postoperative quality of life with minilaparotomy cholecystectomy and laparoscopic cholecystectomy has rarely been compared. Nilsson et al (2004) compared minilaparotomy and laparoscopic cholecystectomy in a study including 1719 patients. In their study the quality of life was slightly better among the laparoscopic group one week after operation, but after one month there were no differences between the two groups. Keus F et al (2008) used SF-36 and GIQLI questionnaires and found no statistically significant difference between the laparoscopic (n=120) and the minilaparotomy cholecystectomy groups (n=137) at 12 weeks postoperatively. In study II, physical role functioning was slightly better after laparoscopic cholecystectomy than after minilaparotomy.

In the long term (study V), most patients in both groups found their quality of life better after than before operation. In conclusion, the quality of life is rather similar after both operations and is therefore an insignificant factor when the choice between minilaparotomy and laparoscopy is made.

6.5 CHOLECYSTECTOMY IN DAY SURGERY (III, IV)

In 1990 Ledet WP Jr (1990) published his series of 200 consecutive cholecystectomies, which were all performed on an outpatient basis. In his study all patients were discharged between 3 and 10 hours after the completion of the surgical procedure and no complications occurred. It is notable that Ledet did not use transverse minilaparotomy incision, but instead made a short (5–10 cm long) vertical incision. Some questions arise from the extremely good results. Were patients really discharged, or was some kind of patient hotel used? Is it possible to do 200 consecutive operations without any minor complications?

Seale AK and Ledet WP Jr (1999) used a transverse 4 to 7cm long minilaparotomy incision, preserving as much of the rectus abdominis muscle as possible. They had 898 minilaparotomy cholecystectomy patients, 89% of whom were discharged in less than 12 hours after the operation. In their series there was a low complication rate (0.2%) and only 0.3% of the day surgery patients were readmitted.

Thomas S et al (2001) used a short (mean 8 cm long) right subcostal incision in their study. They had 30 consecutive patients, 22 of whom were discharged on the operation day. Neither complications nor readmissions occurred in their study.

Although there are some studies where minilaparotomy or short incision open cholecystectomy has been successful when performed as day surgery, the minilaparotomy cholecystectomy has not become a preferred procedure in surgical treatment of cholecystolithiasis.

Results in study III in the day surgery pilot study were promising compared with earlier studies, especially if obese patients are not included. In randomised day surgery series (study IV) there were no significant differences between the two groups in terms of the main outcome. However, the success of day surgery was not as high as reported by other studies. Chronic cholecystitis was one reason for poor outcomes. Day surgery was a new method for cholecystectomy in Kuusankoski District Hospital, and patients were in a normal surgery ward instead of a day surgery unit. If the personnel are not used to handling patients on a day

surgery basis, it might influence the day surgery success. Another important issue is that if patients stay in the normal surgery ward postoperatively, it is easier to stay overnight in the ward, when there is no need to change from day the surgery unit to surgery ward.

In study IV patients who stayed overnight had more nausea and vomiting than patients whose day surgery was successful. One explanation for the nausea and vomiting might be medications which were used in general anaesthesia. There are studies where inhalation anaesthesia with sevoflurane is associated with more nausea and vomiting than total intravenous anaesthesia with propofol (Kim GH et al 2011, Vari A et al 2010). No postoperative nausea and vomiting prophylaxis was used in this study. However, there are several reports indicating that e.g. dexamethasone at i.v. doses of 5-10 mg during anaesthesia may decrease the risk of postoperative nausea and vomiting. Moreover, patients with dexamethasone have less postoperative pain, which is another factor that may hasten the recovery after surgery and improve the discharge readiness in patients with cholecystectomy. (Mataruski MR et al 1990, Baxendale BR et al 1993)

6.6 LONG-TERM OUTCOME (V)

Differences in the long-term outcome between minilaparotomy and laparoscopic cholecystectomy have not been established. McMahon AJ et al (1995) found in randomized controlled trial of 299 patients that the only statistically significant difference was a higher rate of 'heartburn' among the minilaparotomy group. In study V the rate of reflux symptoms was decreased in both groups after the operation. It is difficult to find any reason why cholecystectomy (whatever the technique) could decrease or increase reflux disease.

Ros A et al. (2004) found no significant difference in cosmetic satisfaction and the quality of life between the laparoscopic and the minilaparotomy groups after a one-year follow-up. In earlier reports the issue of symptom relief after cholecystectomy had been relatively poorly addressed. Gui GP et al (1998) evaluated 92 patients who were followed up after cholecystectomy for a mean of 31 months and found that abdominal pain continued to be present, or arose de novo in 28/92 (30%) patients. Abdominal bloating, dyspepsia, heartburn, fat intolerance, nausea and vomiting were significantly improved after cholecystectomy, but diarrhoea, constipation and excessive flatus were not.

In study V, in the follow-up interview, the patients in the laparoscopic group reported significantly more residual abdominal pain than the patients in the minilaparotomy group. This is surprising, as it seems logical to expect no recurrences of pain and symptoms of gallbladder colic when the gallbladder is removed. Especially when the laparoscopic and minilaparotomy procedures are being compared, no differences in the symptom relief are to be expected. The data from our study suggests that in 38% of patients in the laparoscopic group and in 20% of the patients in the minilaparotomy group abdominal symptoms recur after cholecystectomy. The explanation for the high figure of the residual abdominal symptoms after the laparoscopic procedure remains unknown. These finding also indicate how difficult it is to determine 'gallstone specific' symptoms preoperatively. Therefore, symptom relief should become the focus of therapy with the correct diagnosis of symptomatic cholelithiasis and the appropriate indication for cholecystectomy.

Most of the patients in both groups were satisfied with the operation overall, but for some reason the patients in the laparoscopic group were more often ready to recommend the operation for others. It is interesting that the converted patients were satisfied with the overall result as well as the cosmetic results. However, the small number of converted patients in our study makes drawing any firm conclusions impossible.

However, it can be concluded that the long-term outcome is quite similar after minilaparotomy and laparoscopic cholecystectomy. In this study the patients in the minilaparotomy group had fewer residual abdominal symptoms, but some patients expressed dissatisfaction with the cosmetic results.

6.7 MINILAPAROTOMY WITH ULTRASONIC DISSECTION (VI)

Several trials show that based on the short-term outcome, laparoscopic cholecystectomy with ultrasonic dissection could be a feasible technique for elective cholecystectomy (Sietses C et al 2001, Janssen IM et al 2003, Cengiz Y et al 2005, Bessa SS et al 2008, Cengiz Y et al 2009, El Nakeeb A et al 2010, Kandil T et al 2010, Redwan AA 2010, Jain SK et al 2011). The results indicate that ultrasonic dissection leads to a shorter mean operation time (Janssen IM et al 2003, Cengiz Y et al 2005, Bessa SS et al 2008, El Nakeeb A et al 2010, Kandil T et al 2010, Jain SK et al 2011) and a shorter mean hospital stay (Cengiz Y et al 2005, Bessa SS et al 2008, El Nakeeb A et al 2010, Kandil T et al 2010, Jain SK et al 2011), less intraoperative blood loss (Cengiz Y et al 2009, El Nakeeb A et al 2010, Kandil T et al 2010), fewer intraoperative conversions, fewer gallbladder perforations (Janssen IM et al 2003, Cengiz Y et al 2005, Bessa SS et al 2008, Cengiz Y et al 2009, El Nakeeb A et al 2010, Kandil T et al 2010, Jain SK et al 2011), fewer postoperative intra-abdominal fluid collections (El Nakeeb A et al 2010, Kandil T et al 2010) and less bile leakage and postoperative abdominal pain and nausea (Cengiz Y et al 2005, El Nakeeb A et al 2010, Kandil T et al 2010, Jain SK et al 2011).

Cholecystectomy by minilaparotomy or laparoscopy has been shown to have equal results in terms of early recovery in several studies. To my knowledge, ultrasonic dissection is rarely used in minilaparotomy. Therefore the aim of study VI was to investigate the short term outcome after minilaparotomy with ultrasonic dissection.

Xiong J et al (2012) carried out a meta-analysis with 1056 patients in eight randomised controlled studies that compared ultrasonic energy and monopolar electrosurgical energy in laparoscopic cholecystectomy. The conclusion was that ultrasonic energy is as safe and effective as electrosurgical energy and might potentially be safer in laparoscopic cholecystectomy. However, the financial implications of this technical modality need to be established in a cost-effectiveness analysis.

Cengiz Y et al (2005, 2009) found in two randomised studies that ultrasonic dissection in laparoscopic cholecystectomy compared to conventional electrocautery might lead to less blood loss, fewer gallbladder perforations, less pain and nausea and shorter sick leave.

Based on previous studies, ultrasonic dissection seemed attractive to be used in a minilaparotomy procedure, as there have been some good results in laparoscopic cholecystectomy. In study VI the minilaparotomy cholecystectomy group had less early postoperative pain and there was a trend to use fewer analgesics postoperatively and to have a shorter sick leave, a better success rate for day surgery and a faster return to work. Since in the

former studies there was not such a difference between minilaparotomy cholecystectomy and the laparoscopic procedure when using electrocauterisation in both groups, a likely explanation is the use of ultrasonic dissection in the minilaparotomy group. This could be explained by the fact that ultrasonic dissection has been reported to cause less lateral tissue damage with a smaller inflammatory response and less oedema in tissue (Gossot D et al 1999).

Ultrasonic scissors are considered expensive, but in study VI there was no difference between the groups in terms of direct costs of disposable instruments. If patients have improved postoperative recovery (e.g. faster return to work, better success rate of day surgery) when ultrasonic dissection is used, it might be more economical also from the tax payer's point of view. To confirm the advantages of ultrasonic dissections in minilaparotomy cholecystectomy we should also have randomised studies comparing conventional minilaparotomy and ultrasonic dissection minilaparotomy cholecystectomy.

All in all, it seems that minilaparotomy cholecystectomy with ultrasonic dissection causes less early postoperative pain, and it improves the patient's postoperative recovery compared to laparoscopic cholecystectomy with a conventional technique. Thus, the minilaparotomy procedure with ultrasonic scissors is an attractive alternative to conventional laparoscopic cholecystectomy.

6.8 FUTURE PERSPECTIVES

Minimally invasive treatments are spreading rapidly all over the world. Laparoscopic cholecystectomy is the gold standard in the treatment of symptomatic gallstones. Today many elective laparoscopic cholecystectomies are performed on a day surgery basis with fast postoperative recovery and good cosmetic result. It is difficult to develop a new strategy for treating symptomatic gallstones with better results than laparoscopic cholecystectomy. Minilaparotomy cholecystectomy seems to be an equal method with laparoscopic cholecystectomy, and it might be less costly with simple instrumentations as there is no need for disposable instrumentations.

Single-incision laparoscopy and natural orifice transluminal surgery have not convinced surgeons, and both methods seem to require a long learning curve without offering any special benefits compared to conventional laparoscopic or minilaparotomy cholecystectomy. It seems that single-incision laparoscopy and natural orifice transluminal surgery are not revolutions in surgery compared to what laparoscopic surgery was twenty years ago.

Even though robotic surgery is expensive, it has rapidly become popular in some field of surgery (e.g. radical prostatectomy). Robotic surgery has not given any benefit in gallstone surgery, but technological advances in the future may change situation. When new "robots" are developed and become cheaper, they may become more popular in gallstone surgery. Robotic surgery may help the operation in difficult situations. It also gives a possibility to do an immediate "long-distance" consultation during the operation.

According to the result in study VI it seems that ultrasonic dissection might provide better results in minilaparotomy cholecystectomy, but this needs further studies to be confirmed. It is still unclear whether the incision technique in minilaparotomy is important or not. Is it necessary to spare the rectus abdomis muscle, and how long an incision is considered minilaparotomy?

In the future it might be possible to develop better medications for conservative treatment of gallstones, or to prevent gallstones for high-risk patients, both of which, if successful, may decrease the need for the surgical approach. However, this is unlikely in the near future. Therefore, any attempts to improve the outcome for surgical patients are welcome. The most important issue is the patient selection in order to recognise those patients who may benefit from surgery.

7 Summary and Conclusions

Based on the present study the following conclusion can be drawn:

1. In the treatment of symptomatic gallstones minilaparotomy cholecystectomy is as good as laparoscopic cholecystectomy when perioperative and short-term outcome (stay at the hospital, postoperative pain, length of the sick leave, complications) are considered.

2. During short-term recovery there is only a minimal difference in quality of life between minilaparotomy cholecystectomy and laparoscopic cholecystectomy.

3. Minilaparotomy cholecystectomy can be performed on a day surgery basis. In patient selection for day surgery, the possibility of chronic cholecystitis should be noted as a risk factor, and general anaesthesia should be well planned to avoid postoperative nausea and vomiting.

4. Long-term outcome after minilaparotomy and laparoscopic cholecystectomy are quite similar. Different kinds of abdominal symptoms are remarkably common after both procedures.

5. Ultrasonic dissection in minilaparotomy cholecystectomy seems to improve short-term outcomes (postoperative pain, use of analgesics, length of the sick leave) compared with laparoscopic cholecystectomy with monopolar electrosurgical energy.

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Minilaparotomy Cholecystectomy in the Treatment of Gallstone Disease

Comparison with Laparoscopic Cholecystectomy

Cholecystectomy is a common elective surgical procedure and for the last two decades laparoscopic cholecystectomy has been the most commonly used technique. In this thesis, I evaluate the feasibility of minilaparotomy cholecystomy; analysis of data indicates that the recovery after minilaparotomy is similar to that observed after laparoscopic cholecystectomy

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