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Original research

Prophylactic laparoscopic cholecystectomy in adult sickle cell disease patients with cholelithiasis: A prospective cohort study

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HIGHLIGHTS

- Prophylactic cholecystectomy in sick cell disease patient with asymptomatic cholelithiasis is a safe procedure.
- We observed a 4% sick cell disease related morbidity in asymptomatic patients with cholelithiasis who had cholecystectomy.
- In our symptomatic patients, Sick Cell Disease related morbidity was 14%.
- Prophylactic cholecystectomy can reduce sick cell disease related complications.

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ABSTRACT

Introduction: Prophylactic laparoscopic cholecystectomy remains controversial and has been discussed for selected subgroups of patients with asymptomatic cholelithiasis who are at high risk of developing complications such as chronic haemolytic conditions. Cholelithiasis is a frequent condition for patients with sickle cell disease (SCD). Complications from cholelithiasis may dramatically increase morbidity for these patients. Our objective was to evaluate the effectiveness of prophylactic cholecystectomy in SCD patients with asymptomatic gallbladder stones.

Methods: From January 2000 to June 2014, we performed 103 laparoscopic cholecystectomies on SCD patients. Fifty-two patients had asymptomatic cholelithiasis. The asymptomatic patients were prospectively enrolled in this study, and all underwent a prophylactic cholecystectomy with an intraoperative cholangiography. The symptomatic patients were retrospectively studied. Upon admission, all patients were administered specific perioperative management including intravenous hydration, antibiotic prophylaxis, oxygenation, and intravenous painkillers, as well as the subcutaneous administration of low-molecular-weight heparin. During the same period, 51 patients with SCD underwent a cholecystectomy for symptomatic cholelithiasis. We compared these 2 groups in terms of postoperative mortality, morbidity, and hospital stay.

Results: There were no postoperative deaths or injuries to the bile ducts in either group. In the asymptomatic group, we observed 6 postoperative complications (11.5%), and in the symptomatic group, there were 13 (25.5%) postoperative complications.

Discussion: Regarding the SCD complications, we observed 1 case (2%) of acute chest syndrome in an asymptomatic cholelithiasis patient, while there were 3 cases (6%) in the symptomatic group. Vaso-occlusive crisis was observed in 1 patient (2%) with asymptomatic cholelithiasis, and in 4 patients (8%) in the other group. The mean hospital stay averaged 5.8 (4–17) days for prophylactic cholecystectomy and 7.96 (4–18) days for the comparative symptomatic group.

Conclusions: Postoperative complications related to SCD were less frequent for asymptomatic patients who had a laparoscopic prophylactic cholecystectomy. This intervention, if performed with perioperative specific management, is safe and helps avoid emergency operations for acute complications including cholecystitis, choledocholithiasis, and cholangitis. For SCD patients, a prophylactic cholecystectomy reduces hospital stays.

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1. Introduction

In a recent review, asymptomatic cholelithiasis has a benign natural course. Six to 20% of patients develop symptoms during follow-ups of 4–20 years, and less than 5% develops complications [1]. According to the natural history of silent gallstones, in 1993, an NIH Consensus Conference Report considered asymptomatic gallstones as not an indication for prophylactic cholecystectomy [2]. However, these recommendations could be discussed for high-risk subgroups such as patients with sickle cell disease, diabetes mellitus, asymptomatic cholelithiasis associated with common bile duct (CBD) stones, suspected malignancy, and porcelain gallbladder [1,3,4].

Prophylactic cholecystectomy should be considered for SCD patients with asymptomatic cholelithiasis for various reasons: first, a vaso-occlusive crisis and biliary complications could have similar presenting symptoms including fever, abdominal pain, leucocytosis, and jaundice, and a definitive diagnosis and management could be difficult in this situation. Second, the natural history of cholelithiasis in patients with chronic haemolytic anaemia is different from that of the general population in which cholelithiasis affects only 10% of adults. Prevalence increases slowly with age and after the age of 60 years, it increases from 10% to 15% for men and 20%–40% for women with present stones [1]. However, with SCD, cholelithiasis is observed in 70% of adults older than 30 years [5,6]. In fact, the incidence of pigmented stones in patients with chronic haemolytic diseases is frequent, including paediatric patients, and increases with age: 14% for those under 10 years, 22% for those between 10 and 14 years of age, 36% for those between 15 and 18 years of age, and 50% for patients over 22 years of age [7–9]. Third, contrary to the general population in whom 2–5% develop biliary complications during a follow-up of 5–20 years, this risk is higher for SCD patients. Fifty per cent develops complications within 3–5 years of diagnosis [1]. In this specific group, emergency surgery can be associated with high morbidity and mortality [10–13]. The purpose of this study was to show that laparoscopic prophylactic cholecystectomy has a lower morbidity than cholecystectomy performed for symptomatic lithiasis.

2. Materials and methods

The Department of Haematology at the University Hospital Tenon, with about 700 hospitalizations every year, was certified as a reference centre for the management of patients with a major SCD in France (http://www.orpha.net/orphacom/cahiers/docs/FR/Liste des centres de référence labellises.pdf).

From January 2000, along with the haematologists and anaesthesiologists, we decided to evaluate the usefulness of a prophylactic elective laparoscopic cholecystectomy prospectively for adult SCD patients who had asymptomatic cholelithiasis. The prospective management of these asymptomatic patients was carried out over a 14-year period from 2000 to 2014.

Until June 2014, all the 52 adult SCD patients with asymptomatic cholelithiasis who were diagnosed by ultrasound received an operation and underwent a prophylactic cholecystectomy with a routine intraoperative cholangiography. During the same period, we also reviewed the records of 51 other SCD patients who underwent an elective laparoscopic cholecystectomy for symptomatic cholelithiasis. All patients had an ultrasound examination of the gallbladder and biliary tract and were diagnosed with gallbladder cholelithiasis without stones in the CBD, and in both groups, no SCD patients had any common duct stones that were diagnosed preoperatively. Among 52 patients with asymptomatic cholelithiasis, 43 had homozygous sickle cell haemoglobin HbSS; 4 had heterozygous sickle cell haemoglobin HbSC; 4 had thalasso-sickle cell disease; and 1 had associated β-thalassemia. The patients' ages were between 18 and 53 years, with a mean age of 26.5 years. There were 39 females. The mean preoperative haemoglobin level was 8.5 g/dL (range, 6.1–12.6).

In the symptomatic patient group, there were 42 homozygous sickle cell haemoglobin HbSS patients, 6 heterozygous sickle cell haemoglobin HbSC patients, and 3 thalasso-sickle cell disease patients. Their mean age was 25.4 years (range, 18–46), with a total of 36 females. The mean preoperative haemoglobin level was 8.6 g/dL (range, 6–11).

Perioperative management was performed for all patients who had an operation. This management involved a multidisciplinary approach including haematologists, anaesthesiologists, and surgeons. All patients were hospitalized in the Department of Surgery 1 day before the cholecystectomy. Initially, and until 2005, all patients with a haemoglobin level below 10 g/dL received a blood transfusion to achieve a preoperative haemoglobin level of >10 g/dL. Since 2006, exchange transfusion was given only to patients with a haemoglobin level of <7 g/dL. Upon admission, all patients received intravenous hydration, which was continued until the patients were able to drink 2 L of water independently per day. Intravenous antibiotic prophylaxis with amoxicillin or penicillin was started 1 h before the cholecystectomy and was continued for 5 days post-operation. Further, additional interventions included the following: oxygenation incentive spirometry use; intravenous painkillers were continued on an oral basis; the subcutaneous administration of low-molecular-weight heparin in preventive doses during the postoperative period; and early mobilization.

During the same study period, we have also operated on 2 emergency patients, 1 for acute cholecystitis and the other for cholangitis with CBD stones. This was the only patient who had CBD stones diagnosed preoperatively by ultrasound. He was excluded because our objective was to evaluate the treatment of asymptomatic gallbladder lithiasis without complications. Emergency procedures were not included in this study.

Laparoscopic cholecystectomy was carried out under general anaesthesia and with the application of a thermal cover at 40 °C for the entire operative period. The pneumoperitoneum was made through an umbilical incision or in the left hypochondrium with subsequent introduction of a 10-mm trocar for insufflation of carbon dioxide at a pressure of 12 mmHg. Laparoscopic cholecystectomy was performed using a standard 4-port technique. Cholangiography was routinely performed by injection of iodinated contrast (Hexabrix 320 mg/mL) into the biliary tract through a percutaneous catheter with a 20-F-diameter rigid tip (Applied Medical, USA) and introduced in the cystic duct by using a cutaneous incision in the right hypochondrium. Opacification of the CBD, as well as the passage of contrast into the duodenum, has been confirmed through a radioscopy handset available in the operating room. If stones were found in the CBD, they were removed by introduction of a Dormia basket (or with jets of a saline solution under high pressure in the bile duct after choledochotomy), so as to spill the stones from cystic duct. Only if it was impossible to extract the stones from the CBD, a conversion to an open cholecystectomy and a choledochotomy was performed to complete the stone extraction. In these cases, a T-tube was left in place.

We compared the results observed in the 2 patient groups that received an elective operation, in terms of postoperative mortality, morbidity, and days of hospital stay. The outcome was correlated in both groups. Both groups used a χ^2 test to compare their preoperative and postoperative characteristics. P values of <0.05 were considered statistically significant. We report our observational studies according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): http://www.sciencedirect.com/science/article/pii/S174391911400212X.

3. Results

In the group of patients with asymptomatic cholelithiasis, 11 (21%) patients received a preoperative blood transfusion, and an exchange transfusion was carried out in 5 patients preoperatively (10%). Four patients (8%) received a post-operative blood transfusion. In this group, gallstones were found in the CBD in 1 case (2%). In this case, it was necessary to convert from a laparoscopic to open cholecystectomy to perform a choledochotomy and to complete the extraction of 4 stones in the CBD. There were 6 post-operative complications (11.5%). A re-intervention using a right subcostal incision was necessary for 2 cases because of post-operative hemoperitoneum: 1 patient was administered anticoagulant therapy for 4 years because of mechanical mitral valve prosthesis (Coumadin was stopped 5 days before surgery and replaced by low-molecular-weight heparin at a dose of 0.6 mL, twice per day, to obtain an INR of <1.5). The second hemoperitoneum occurred because of displacement of the titanium clip on the cystic artery. The 2 cases requiring an open re-exploration for hemoperitoneum are explainable as follows: the first case had a high bleeding risk because of a metallic cardiac valve prosthesis, and the second case may have been related to a technical error in the positioning of a clip. Other complications included: 1 acute chest syndrome case, 1 *Klebsiella pneumoniae* case, 1 abdominal vaso-occlusive crisis case, and 1 postoperative jaundice case (that required imaging investigations; EUS was subsequently performed; and no stone was revealed probably secondary to spontaneous migration). There were no bile duct injuries or deaths. The mean hospital stay was 5.8 (range, 4–17) days.

In the group of patients with symptomatic cholelithiasis, 3 patients had acute cholecystitis previously, and the other 2 patients had acute pancreatitis that was treated medically. They were operated on electively after the resolution of the acute episode. A total of 4 patients received a preoperative blood transfusion (8%). An exchange transfusion was performed for 5 patients (10%), and 3 patients received a postoperative blood transfusion (6%). An intraoperative cholangiography showed 8 cases had stones in the CBD. We have treated 3 cases of lithiasis by laparoscopy, and for 5 cases, a conversion from a laparoscopic to open cholecystectomy was performed with a choledochotomy to complete the extraction of CBD stones. For 4 cases, we left a T-tube; in 1 case, 1 trans-cystic drain was removed 1 month after surgery. There were 13 (25.5%) postoperative complications. For 11 cases, there were medical complications: 3 acute chest syndrome cases, 1 *K. pneumoniae* pneumopathy case with acute respiratory failure, 4 vaso-occlusive abdominal crisis cases, and 1 septic shock case with the identification of *Escherichia coli* in the blood culture, while 2 cases had fever without identification of an infectious source. The surgery-related complications included 1 case that required percutaneous radiological drainage of an abscess in the gallbladder fossa and 1 case of a haematoma on the abdominal wall. It was necessary to monitor 4 patients in the intensive care unit; 3 patients were transferred to the Department of Haematology for close observation and treatment.

There were no bile ducts injuries or deaths. Further, the mean hospital stay for the symptomatic patients was 7.96 (4–18) days.

4. Discussion

In literature, it has been reported that a series of laparoscopic cholecystectomies has been performed in adult patients with SCD, and in almost all cases, it was for symptomatic cholelithiasis [14–22]. In these series, few cases of asymptomatic gallstones were included, ranging from 1 [17] to 5 [18], but none of them have been separately studied.

For children with SCD and cholelithiasis, some authors suggested the benefit of laparoscopic cholecystectomy in asymptomatic patients. Suell reported on 13 cholecystectomies in asymptomatic children [5]. Currò et al. proposed an intervention in 30 asymptomatic children with cholelithiasis. The operation was accepted and performed for 16 children [23]. Since 2005, in France, the High Authority of Health recommended a laparoscopic cholecystectomy for SCD children with a diagnosis of gallstones, even if asymptomatic (http://www.hassante.fr/portail/upload/docs/application/pdf/Drepanocytose_reco.pdf). However, in SCD adults, there are no guidelines for the management of asymptomatic cholelithiasis. To our knowledge, our prospective study is the first in medical literature that analysed a large series of adult SCD patients who underwent laparoscopic cholecystectomy for asymptomatic cholelithiasis.

The natural history of cholelithiasis in sickle cell patients seems different than that of the general population. Lithiasis occurs at a younger age, and 70% of silent gallstones in SCD patients become symptomatic leading to delayed cholecystectomy [12,13]. We hypothesized that prophylactic cholecystectomy may diminish SCD related complications that were observed in patients who had elective operations for symptomatic cholelithiasis or emergency operations.

We observed no post-operative deaths in either group. The perioperative management that was performed may explain these results. However, some series reported in literature included symptomatic and complicated cholelithiasis and reported a post-operative mortality of 1%–6% [10,18,22]. For SCD patients, it has been reported that emergency cholecystectomy is associated with a high incidence of complications and a high postoperative risk [24,25].

For the SCD patients, we decided to perform systematic intra-operative cholangiography, however for the general population and non-SCD patients, we only performed selective operative cholangiography using a valid multifactorial score that we established [26,27]. The main reason was to differentiate the symptoms of a residual choledocolithiasis from a sickle cell crisis during the early postoperative period [28]. This eliminates the risk of unnecessary bile duct exploration in emergency situations in case of jaundice post-cholecystectomy. Nickkholgh et al. showed that performing an intraoperative cholangiography routinely during laparoscopic cholecystectomy is a safe and accurate procedure for the identification of stones of the biliary tract [29].

Cholangiography showed a high rate (16%; *P* value of 0.02) of associated choledocholithiasis in the group of symptomatic patients. In a series of 1000 cholangiography patients in the general population, the incidence of choledocholithiasis was only 5% [30]. Thus, in our population of SCD patients with symptomatic gallstones, associated choledocholithiasis was 3 times more elevated. The incidence of CBD stones in SCD patients has been reported to reach 30% [31,32]. This suggests a different gallstone disease. In most patients in our series, we found microlithiasis with pigmented gallstones. The size of the gallstones could explain a more frequent migration into the main biliary tract. In the group of asymptomatic gallstones patients, the choledocholithiasis rate was only 2%, even though the mean age in both groups was similar, implying that age was a predictive parameter [26,27].

Regarding the treatment of associated choledocholithiasis, if the CBD stones could not be laparoscopically removed, we converted to an open operation, as opposed to a postoperative ERCP, because we preferred to avoid potential risks associated with ERCP and sphincterotomy such as in pancreatitis, bleeding, cholecystitis, perforation, and stenosis. Some studies reported that laparoscopic CBD exploration has a lower morbidity and mortality rate (7% and 0.19%, respectively) than 2-stage management with ERCP and sphincterotomy (13.5% and 0.5%, respectively) in the management

of incidentally discovered CBD stones [33]. The second main reason for preferring a conversion to an open operation, instead ERCP, is to avoid a second anaesthesic induction during the subsequent procedure to complete the CBD extraction by ERCP. Anaesthesia may be risky for a SCD patient. Many studies have demonstrated the advantages of a laparoscopic technique over an open cholecystectomy, including a better postoperative pulmonary function [34], less postoperative pain [35], a shorter hospitalization, and a faster recovery.

The long postoperative length of stay in both groups is explainable by the application of our protocol that includes intravenous hydration, oxygenation, and prophylactic postoperative antibiotics for 5 days. The second reason to explain this length of stay is a great caution for SCD patients, who need a close observation to prevent and to treat early SCD-related complications. In fact, we observed all cases of acute chest syndrome and vaso-occlusive crisis in our patients, during the first postoperative week. The French High Authority of Health recommends penicillin prophylaxis for SCD children for all surgical procedures (/www.hassante.fr/portail/upload/docs/application/pdf/Drepanocytose_reco.pdf). In medical literature, it has been reported and accepted that prophylactic penicillin significantly reduces the risk of pneumococcal infection in SCD patients, but the optimal duration of antibiotic treatment remains unknown [36,37].

Medical complications related to SCD were more frequent in symptomatic patients (Table 1), in which there were 3 cases of acute chest syndrome, as opposed to a single case in the asymptomatic patient group. Consequently, we observed 1 sickle cell crisis with asymptomatic lithiasis, as opposed to 4 cases in the symptomatic group.

Nevertheless, the groups were similar in mean age (26.5 vs 25.4 years), sex distribution (13M/39F vs 15M/38F), and mean haemoglobin preoperative level (8.5 vs 8.6 g/dL). All patients received an elective procedure and had perioperative management. However, although the mean Hb level was the same (8.5 versus 8.6 g/dL) in both groups, the asymptomatic patients had more preoperative transfusions or exchange transfusions than the group of patients with symptomatic gallstones (16/52 versus 9/51). This is because of the greater caution considered for the asymptomatic group, as compared with the symptomatic group for which there was no question of a surgical indication, and this may explain the lower morbidity rate. There is no agreement regarding the necessity for blood transfusion in patients with SCD before cholecystectomy. Aziz et al. showed that laparoscopic cholecystectomy could be safely conducted without a preoperative blood transfusion and without complications [38]. In the January 2013 *Lancet*, Howard et al. published a randomized, controlled, multicentre study and demonstrated that with low- and medium-risk surgery, preoperative transfusions are associated with a significantly decreased risk of postoperative complications in patients with homozygous SCD, especially concerning acute chest syndromes [39]. In our experience, we have transfused or performed an exchange transfusion for patients with haemoglobin levels of <7 g/dL.

We observed a 4% SCD-related morbidity in asymptomatic patients. This rate is lower than that reported in medical literature for symptomatic patients [22,39,40]. In our symptomatic patients, SCD-related morbidity was 14%. The higher rate of SCD-related postoperative complications could also be explained by a longer operative time in this group. We had 2 complications related to surgery in each group, but without any biliary injuries. Unfortunately, surgically related complications were more severe in the asymptomatic group. Two patients required a laparotomy for haemostasis; they did not develop a postoperative chest syndrome or vaso-occlusive crisis.

5. Conclusions

This series of 103 elective cholecystectomies included a group of 52 asymptomatic adults with SCD and cholelithiasis; to our knowledge, this study comprised the greatest number of asymptomatic SCD patients studied after a cholecystectomy. For asymptomatic lithiasis our results showed that a prophylactic cholecystectomy is a safe procedure and has less postoperative medical complications.

Table 1
Outcomes of 103 laparoscopic cholecystectomies in adults with SCD.

103 Patients	Group of 52 SCD patients with asymptomatic cholelitiasis	Group of 51 SCD patients with symptomatic cholelitiasis	P value < 0.05
Age	26.5 (18–53)	25.4 (18–46)	
Male/Female	13/39	15/36	
Preoperative Hb level g/dl	8.5 (6.1–12.6)	8.6 (6–11)	
Preoperative Transfusions	11/52 (21%)	4/51 (8%)	0.09 NS
Preoperative Exsanguino-exchanges	5/52 (10%)	5/51 (10%)	0.97 NS
Postoperative Transfusions	4/52 (8%)	3/51 (6%)	0.73 NS
Choledocholithiasis	1/52 (2%)	8/51 (16%)	**0.02**
Conversion to open for choledocholithiasis	1/52 (2%)	5/51 (10%)	
Total morbidity	6/52 (11.5%)	13/51 (25.5%)	0.12 NS
Complications related to SCD	2/52 (4%)	7/51 (14%)	0.10 NS
Sickle cell crisis	1/52 (2%)	4/51 (8%)	
Acute chest syndrome	1/52 (2%)	3/51 (6%)	
Other medical complications			
Klebsiella pneumoniae	1/52 (2%)	1/51 (2%)	0.41 NS
Postoperative jaundice	1/52 (2%)	0	
Fever	0	2	
Septic shock	0	1	
Surgery-related complications	2/52	2/51	
Hemoperitoneum	2/52 (4%)	0	0.98 NS
Post-cholecystectomy abscess	0	1 radiological drain	
Abdominal wall haematoma	0	1	
Mortality	0	0	
Mean hospital stay (days)	5.8 (4–17)	7.96 (4–18)	0.56 NS

Statistical Analysis Outcomes from 2 Groups (χ^2 test; $P < 0.05$). NS, non-significant.
The bold represents the differentiate postoperative complications related to sickle cell disease from other medical complications and surgery related complications. About the numbers, 0.02 is in bold because it is a *P* significant value.

Conflict of interest

None.

Funding

None.

Ethical approval

No animals activities were performed – ethical approval not needed.

Author contribution

Dr Muroni conceived the idea, wrote the manuscript and performed the literature search.

Dr Loi assisted the literature search and contributed to the acquisition, analysis and interpretation of data.

Dr Lionnet contributed to the conception of the study acquisition of data.

Pr. Girot contributed to the conception of the study and revision of the manuscript.

Pr. Houry contributed to the conception of the study; interpretation of data, literature search revision of the manuscript and provided final approval of the manuscript.

Guarantor

Dr. Mirko Muroni.

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