RESEARCH PAPER

Perioperative Events of Laparoscopic Cholecystectomy in Patients with Hemoglobinopathies

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Abstract

Background: Hemoglobinopathies are common genetic disorders affecting the synthesis of one of the globin chains of hemoglobin molecule. Laparoscopic cholecystectomy is the standard procedure for treatment of patients with normal hemoglobin and symptomatic gall stones, but doubt is still to date regarding safety of this procedure in patients with hemoglobinopathy.

Aims: 1. To assess the safety of laparoscopic cholecystectomy for hemoglobinopathic patients, 2. To describe the perioperative events that might happen before, during or after this procedure.

Patients and Methods: This is a record-based comparative study conducted over a period of seven years, involved 62 hemoglobinopathic patients and 148 patients with normal hemoglobin variant. All underwent laparoscopic cholecystectomy and comparison done regarding perioperative events.

Results: The overall complication rate was 56.5% in hemoglobinopathic patients and 21.6% in the other group and the difference was statistically significant (P- value <0.001). Vaso-occlusive crisis occurred in 9 patients (14.5%), respiratory complications (atelectasis and bronchitis) in (9.7%), acute chest syndrome in (4.8%) and hemolysis in (4.8%).

Conclusions: 1. Laparoscopic cholecystectomy is safe in well prepared hemoglobinopathic patients but it is associated with significantly higher rate of disease related complications, namely acute chest syndrome, hemolysis and vaso-occlusive crises.2- Hemoglobinopathic patients require special pre, intra and post-operative care which should be offered by the surgeon, the physician and the anesthetist

Keywords: hemoglobinopathies, laparoscopic cholecystectomy, sickle cell disease, complications.

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Introduction

Hemoglobinopathies are one of the most common autosomal recessive disorders worldwide;[1] mainly present in two patterns, either qualitative disorders (HbS) in which valine replacing glutamine in the 6th position of Beta chain, or quantitative (reduction or deletion) of either Alpha or Beta chain.[2] This results in abnormal hemoglobin molecule which is the cause of chronic suffering of the patient. Hemoglobin S-Beta-thalassemia which results from carrying the genes of both thalassemia and sickle cell disease may present with severe form of disease than either alone. [3] The treatment of hemoglobinopathic patients constitutes a worldwide concern and thalassemia became a disease of international importance due to travelling and immigration of people. Early and regular blood transfusion and iron chelation have made a dramatic increase in survival of

thalassemic patients to adulthood. These patients may need surgical treatment so that surgeons and anesthetists have to be familiar with the physiological abnormalities and the high possibility of perioperative complications.[4] The incidence of cholelithiasis differs in different types of hemoglobinopathies; 4-85% in sickle cell anemia, 29% in Sickle Cell trait, 12% in Hemoglobin S-Beta-thalassemia disease and 30-> 80% in β-thalassaemia Major.[5] Hemoglobinopathies are worldwide disease. More than 30 million people from 163 countries suffer from sickle cell disease (SCD).[6] About 1.5% of the world population are carriers of Beta-thalassemias. New surveys stated that 300,000-400,000 babies are found to have a serious hemoglobin disorder yearly.[7] In Arab countries, Beta thalassemia carrier rates are 1-11%.[2] In Iraq; hemoglobinopathies are still considered as a challenge. In Basrah, Beta thalassemia carriers are 4.6% of the population,[2] while the prevalence of sickle cell disease is 16%. [8] Hemoglobinopathic patients may require surgeries during their lifetime and general anesthesia for these patients is a risky procedure; so specific pre, intra and postoperative measures should be taken like avoidance of hypoxia, adequate hydration, temperature control and correction of anemia. Cholecystectomy is one the most frequent surgical procedures needed for these patients. This study spots the light on the perioperative facts and events of a spectrum of inherited diseases of hemoglobin in comparison with persons with normal hemoglobin.

PATIENTS AND METHODS

This record-based comparative study was conducted in two tertiary hospitals in Basrah/Iraq, Al Sadr Teaching Hospital and Al Fayha Teaching Hospital. Two hundred and ten patients were included in the study; 62 patients were cases of hemoglobinopathy and 148 were patients with normal hemoglobin from January 2012 till January 2019. Matching of the two groups had been done regarding age and gender. Indications of surgery were chronic calculous cholecystitis and biliary colic. Patients with acute cholecystitis, obstructive jaundice and those with severe comorbid disease making them unfit for general anesthesia were excluded from the study. Hemoglobinopathic patients were diagnosed by hemoglobin electrophoresis. They were investigated by doing blood count, liver function, bleeding profile, blood sugar, renal function screening for hepatitis and HIV, electrocardiography, chest x-rays and abdominal ultrasonography. Echocardiography and respiratory function test were done whenever necessary. After outpatient assessment, all patients were admitted one day before surgery except those with hemoglobin level less than 9 g/dl. These cases were admitted earlier for blood transfusion. On admission they were rehydrated by intravenous fluids (1000-1500 ml of 4% DW in 0.18 NS in the evening before surgery) and they received prophylactic antibiotics. All subjected to general anesthesia. Laparoscopic cholecystectomy was achieved by classical four ports method. Operative time was recorded from primary port entrance to wound closure. Critical view of safety was the method of gall bladder dissection. Drain tube was inserted whenever indicated. Post operatively, patients were managed in the surgical wards (few cases were admitted to the intensive care unit), they received intravenous fluids, antibiotics and analgesia. They were discharged home when they were fully ambulated and started oral diet. Postoperative follow up was extended for three weeks. The study was approved by the ethical committee of The College of Medicine / University of Basrah. Data were analyzed by the use of Statistical Package for Social Sciences (SPSS) software

version 23 using X2 test or Fisher Exact Test. P value of less than 0.05 was considered significant.

RESULTS

The total number of the studied patients was 210, 62 of them had hemoglobinopathy and 148 had normal hemoglobin. Male: female ratio was 1:3.6, mean age was 30.6 years (± 8.58). Both were comparable regarding age and gender (Table-1). Hemoglobin S- Beta-Thalassemia disease constitutes the biggest group of the studied hemoglobinopathic patients (29 cases) (46.8%), followed by patients with sickle cell disease (16 cases) (25.8%). Eight hemoglobinopathic patients had sickle cell trait (12.9%), 4 cases had beta thalassemia minor (6.5%), three had beta thalassemia major (4.8%) and two had alpha thalassemia major (3.2%).

Table 1. Characteristics of hemoglobinopathic Patients and patients with normal hemoglobin.

Age (years)	Hemoglobinopathic patients No. (%)	Patients with normal hemoglobin No. (%)	Total No. (%)	P value
< 30	34 (54.8)	63 (42.6)	97 (46.2)	0.275
30-39	20 (32.3)	63 (42.6)	83 (39.5)	
≥40	8 (12.9)	22 (14.8)	30 (14.3)	
Gender				
Male	14 (22.6)	32 (21.6)	46 (21.9)	0.506
Female	48 (77.4)	116 (78.4)	164 (78.1)	
Total	62 (100)	148 (100)	210 (100)	

Viral markers for hepatitis B were positive in 3.2% of hemoglobinopathic patients and those for Hepatitis C were positive in 6.5%, the difference was statistically significant for hepatitis C only. There was no significant difference between the two groups regarding indication for surgery while there was significant difference between the two groups regarding mean level of hemoglobin and total serum bilirubin and preoperative blood transfusion, (Table-2).

Table 2. Preoperative workup and indications for surgery

Positive viral markers	Hemoglobinopathic patients No. (%)	Patients with normal hemoglobin No. (%)	P value
Hepatitis B	2 (3.2)	0 (0)	0.08
Hepatitis C	4 (6.5)	0 (0)	0.007
No. of Stones (U/S)			0.278
Single	11 (17.7)	20 (13.5)	
Multiple	51 (82.3)	128 (86.5)	
Hemoglobin(g/dl)	9.34	12.23	< 0.001
Preoperative Transfusion	18 (29)	2 (1.4)	< 0.001
Total Serum Bilirubin(mg/dl)	3.63	0.85	< 0.001
Indication for Surgery			
Chronic Calculous Cholecystitis	51(82,3)	130 (87.8)	0.095
Biliary Colic	11 (17.7)	18 (12.2)	

The comparison of intraoperative events showed a higher rate of use of drains in hemoglobinopathic patients and the difference was significant; however there was no significant difference in the mean operative time or the conversion rate (Table-3).

Table 3. Operative Events.

	Hemoglobinopathic patients (62) No. (%)	Patients with normal hemoglobin (148) No. (%)	P value
Conversion Rate	2 (3.2)	2 (1.4)	0.06
Use of Drai	31 (50)	32 (21.6)	< 0.001
Mean Operative Time (minutes)	42.73 Std. Deviation 8.57	38.22 Std. Deviation 9.34	0.523

(Table-4), describes the post-operative complications and hospital stay. There was no significant difference in occurrence of

complications between the two groups except for acute chest syndrome, joint pain, hemolysis and chest pain, they occurred more frequently in hemoglobinopathic patients. There was a significant difference in the overall complication rate between the two groups. The mean hospital stay was significantly longer for hemoglobinopathic Patients than that for patients with normal hemoglobin.

Table 4. Post-operative Events.

	Hemoglobinopathic patients No. (%)	Patients with normal hemoglobin	P value
Joint Pain	10 (16.1)	0 (0)	< 0.001
Chest Pain	4 (6.5)	1 (0.7)	0.027
Acute Chest Syndrome	3 (4.8)	0 (0)	0.025
Hemolysis	3 (4.8)	0 (0)	0.025
Respiratory complications	6 (9.7)	7 (4.7)	0.149
Fever	5 (8.1)	6 (4.1)	0.194
Diffuse abdominal pain	4 (6.5)	6 (4.1)	0.335
Bile leak	0 (0)	2 (1.4)	0.496
Bleeding	0 (0)	4 (2.7)	0.244
Wound infection	0 (0)	6 (4.1)	0.119
Overall complications rate	35 (56.5)	32 (21.6)	< 0.001
Hospital stay (days)	Mean	Mean	< 0.001
	2.27 (Std Deviation 0.79)	1.31 (Std Deviation 0.55)	

Postoperative Complications of hemoglobinopathic patients:

Out of 62 hemoglobinopathic patients, 35 developed different postoperative complications (The overall complication rate is 56.5%). Joint pain occurred in 10 patients, it occurred in the group of patients with sickle cell trait, sickle cell disease and hemoglobin S- Beta-Thalassemia disease equally (3 cases in each group), and one case in Beta thalassemia major group. The three cases who developed acute chest syndrome were patients with sickle cell disease. Three patients developed hemolysis, one of them had sickle cell disease, the second had sickle cell trait and the third had Hemoglobin S- Beta-thalassemia disease. Four patients developed chest pain, another 4 developed diffuse abdominal pain and six patients developed respiratory complications (atelectasis or bronchitis).

DISCUSSION

Laparoscopic cholecystectomy is a well-known procedure for treatment of gall stone disease in patients with normal hemoglobin,[9] but in hemoglobinopathic patients, there is still some debate about safety and feasibility of this procedure.[10,11] Preparation of hemoglobinopathic patients for surgery is quite different: anemia is common because of hemolysis, immunity is compromised and they are liable for vaso-occlusive crisis. Due to the improvement in medical care, patients survive to adulthood therefore facing complications of the disease. Optimum preoperative hemoglobin level and necessity for preoperative transfusion to decrease perioperative morbidity and mortality is still a controversial issue and surgeons should be aware about history of previous transfusions which may indicate the possibility of iron deposition sequelae. In a multicenter study that was done by Vichinsky et al which included 604 patients with sickle cell anemia who underwent different operative procedures, more than one third of

them underwent cholecystectomy they found that there is no difference between aggressive and conservative transfusion regimens.[12] In a retrospective study that had been done in Bahrain on 85 patients with sickle cell disease who underwent different surgeries, they compared the impact of exchange transfusion against simple transfusion and non-transfusion. They found no superiority of exchange transfusion in preventing postoperative sickle cell related complications,[13] while Maigatari, et al found that preoperative transfusion decreases the risk of postoperative sickle related complications in low and medium risk surgical procedures. [14] Vaso-occlusive crisis is the leading cause of readmission for patients with sickle cell anemia is characterized by painful episodes mainly involving bones and joints and abdomen. It is ischemic pain due to precipitation of sickle cells in the microvasculature. The goal of treatment is adequate hydration, analgesia, and blood transfusion. [15] In our study, vaso-occlusive crisis which is presented by bone pain, joint pain and backache was the commonest complication; it occurred in 9 patients (14.5%) postoperatively in spite of adequate pre and intra-operative hydration. All were managed by intravenous fluids and analgesia and improved within 1-2 days. Respiratory complications (atelectasis and bronchitis) were the second most common complication in hemoglobinopathic patients in our series (9.7%). These complications are the most frequent post-operative sequel in a study done by Meshikhes, et al in Saudi Arabia from October 1992 to December 1996, happened in 6 out of 10 patients who developed post-operative complications. [16] Restrictive lung diseases is the usual respiratory abnormality in beta thalassemia major. [17] In addition lung fibrosis and interstitial edema that attributed to iron overload have been considered as causes of restrictive pattern, [18] furthermore anesthetic difficulties and susceptibility to infection are added causes. Acute chest syndrome occurred in (4.8%) of our series of hemoglobinopathic patients especially in patients with sickle cell disease and this was significantly different from patients with normal hemoglobin. All were managed successfully in the intensive care unit. This is consistent with the findings of a retrospective study on patients with sickle cell disease who underwent cholecystectomy, the study achieved in France and published in 2008. This study found a higher mortality after laparoscopic versus open cholecystectomy in patients with sickle cell disease due to a higher rate of occurrence of acute chest syndrome in laparoscopic group (8.5 % Vs. 1.1%).[19] Acute chest syndrome is a common cause of postoperative death in sickle cell disease patients characterized by fever, dyspnea, cough and chest pain with new lung infiltration on chest radiograph after exclusion of atelectasis.[20] Hemolysis is a well-known complication of sickle cell disease. Three cases (4.8%) presented with hemolysis post operatively: pallor, tea colored urine and reduction of hemoglobin level below 9 g/dl. One with sickle cell disease, one with sickle trait and one with sickle cell beta thalassemia. All were managed successfully with RBCs transfusion and discharged well. In our study, preoperatively, a number of hemoglobinopathic patients are found to have viral hepatitis B (3.2%) or hepatitis C (6.5%), so the medical staff should be aware of exposure to a risk of transmission of viral hepatitis as these patients had acquired the infection from previous transfusions.[4] A surprising high rate (67.3%) of positive hepatitis C virus antibodies was reported in Iraqi study published at 2006 in thalassemic patients with a history of repeated transfusions. [21] The mean operative time was 42.73 min for hemoglobinopathic patients and 38.22 min for patients with normal hemoglobin. In other two studies Dan et al and Diarra et al, the mean operative time for patients with sickle cell anemia

was 27.9 and 71.4 minutes respectively. Rachid, et al reported a mean operative time of 64 minutes for patients with sickle cell disease. [19,22,23] Conversion to open cholecystectomy occurred in 2 hemoglobinopathic patients (3.2%) due to limited operative field in relation to big liver and spleen and difficulty to reach an dissect the triangle of Callot .In the normal Hemoglobin variant group, 2(1.4%) cases were converted to open cholecystectomy. In both cases difficulty to dissect in Callots triangle because of fibrosis and scarring was the cause of conversion. A similar conversion rate (4.2%) was recorded by Sani Rachid in Niger in a study published at 2009.[23] However Dan , et al recorded no conversion in a series of 19 patients with sickle cell disease.[22] In our study, abdominal drains were used whenever necessary especially in cases of bleeding and/or difficult dissection in Callots triangle or in liver bed. Drains had been used in approximately half of hemoglobinopathic patients and this was significantly higher than the control group for two reasons: firstly, because of difficult dissection in the presence of hepatosplenomegaly in thalassemic patients and secondly because most hemoglobinopathic patients in the early post-operative period are already jaundiced, tachycardiac owing to hyperdynamic circulation, they have pallor and abdominal pain, so the anticipation of major postoperative complications like bleeding and biliary injury are difficult to diagnose clinically in the presence of these features. The use of drains in laparoscopic cholecystectomy is a matter of debate till now, in a study done by Gurusamy et al, they analyzed the results of six trials involving 741 patients and concluded that drains increase hospital stay and the rate of wound infection. [24] The mean hospital stay differs in different studies, for Dan et al study it was 2.5 days, Diarra, et al 7.7 days for patients with sickle cell disease, while for Rachid et al, the mean hospital stay was 3.5 days. [19,22,23] In our study the mean hospital stay was 2.27 days, it was significantly longer than the that of patients with normal hemoglobin variant (1.3 days)

In a study done by Leandros et al comparing laparoscopic and open cholecystectomy for patients with sickle cell disease. Complications occurred in 5% of laparoscopy group and 20% of open group, the conversion rate was 5%. [25] In Sri Lanka, a retrospective case control study had been done on 450 patients; they found a higher perioperative complication in thalassemic compared with non thalassemic patients.[11]

CONCLUSIONS

1. Laparoscopic cholecystectomy is relatively safe in well prepared hemoglobinopathic patients but it is associated with significantly higher rate of disease related complications, namely acute chest syndrome, hemolysis and vaso-occlusive crises.
2. Hemoglobinopathic patients require special pre, intra and post-operative care which should be offered by the surgeon, the physician and the anesthetist

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الأحداث المحيطة بعملية استئصال المرارة بالمنظار لدى مرضى اعتلال خضاب الدم

الملخص: تعد اعتلالات خضاب الدم من الأمراض الوراثية الشائعة التي تؤثر على تخليق أحد سلاسل الجلوبين في جزيء الهيموغلوبين. ان استئصال المرارة بالمنظار هو الإجراء المعتاد لعلاج المرضى ذوي الهيموغلوبين الطبيعي عند معاناتهم من أعراض حصوات المرارة، ولكن لا يزال هناك شك حتى الآن فيما يتعلق بسلامة هذا الإجراء في المرضى المصابين باعتلال خضاب الدم. تهدف هذه الدراسة الى تقييم خطورة اجراء عملية استئصال المرارة بالمنظار لدى مرضى اعتلال خضاب الدم ووصف الأحداث المحيطة بهذه العملية

الطريقة: هذه دراسة مقارنة أجريت على مدى سبع سنوات، وشملت 62 مريضا يعانون من اعتلال الخضاب و 148 مريضا لديهم الهيموغلوبين الطبيعي. خضع الجميع لعملية استئصال المرارة بالمنظار وتمت المقارنة فيما يتعلق بالأحداث المحيطة بالجراحة.

النتائج: كانت النسبة الكلية للمضاعفات (56.5%) لدى مرضى اعتلال خضاب الدم و(21.6%) لدى المرضى ذوي االهيموغلوبين الطبيعي وان الاختلاف معتد احصائيا (**P value < 0.001**) .حدثت الأزمات الأنسدادية الوعائية في 9 مرضى (14.5%), المضاعفات التنفسية (انخماص) (انكماش رئوي و التهاب القصبات) حدثت في 9,7% و حدثت متلازمة الصدر الحاد في 4,8%.

الاستنتاجات: 1. تعتبر عملية استئصال المرارة بالمنظار لدى مرضى اعتلال خضاب الدم امنة ولكنها معرضة لنسبة عالية من المضاعفات المتعلقة بمرض اعتلال خضاب الدم وبالأخص متلازمة الصدر الحاد وأزمات انحلال الدم و الأزمات الانسدادية الوعائية. 2. يحتاج مرضى اعتلال خضاب الدم الى عناية طبية خاصة يشترك فيها الجراح والمخدر واختصاصي الأمراض الباطنة قبل واثناء وبعد اجراء العملية الجراحية.

الكلمات المفتاحية: اعتلال خضاب الدم, استئصال المرارة بالمنظار,فقر الدم المنجلي, الأحداث المحيطة بالعملية.