Hypoalbuminemia as a risk factor for difficult laparoscopic cholecystectomy

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Original Article

GENERAL SURGERY

OPEN ACCESS

Abstract: Cholelithiasis is one of the most common pathologies of the digestive tract, its incidence is affected by factors such as ethnicity and gender among others. Difficult laparoscopic cholecystectomy refers to the surgical removal of the gallbladder when there are some associated conditions of the same organ or its neighboring organs or of the patient, which do not allow an easy, rapid and comfortable dissection of the gallbladder. Hypoalbuminemia is a decrease in the level of intravascular albumin <3.6 g/dL. Potential mechanisms for hypoalbuminemia include decreased liver disease synthesis, protein malnutrition, increased tissue catabolism, protein-losing enteropathy or change in distribution. Material and method. The Laparoscopy Department of General Hospital 450 was consulted, to request a list of the 692 patients who underwent laparoscopic cholecystectomy from 2012 to 2019. Results. The prevalence of hypoalbuminemia in postoperative patients of laparoscopic cholecystectomy in the General Surgery Service from 2012 to 2019 is 12.7%. Hypoalbuminemia is related to an increase in the conversion rate to open surgery Chi2 = 20.68 p-value = 0.000 OR = 8.10 95% CI [6.6 - 9.8]. Discussion. In our study we found an association of hypoalbuminemia with the presentation of difficult laparoscopic cholecystectomy Chi2 = 6.1 p-values = 0.013 OR = 1.76 95% CI [1.1 - 2.7] as well as with the presence of difficult vesicle, intraoperative bleeding, need to administer antibiotic intraoperatively, Penrose drainage placement, longer surgical time and conversion to open cholecystectomy.

Keywords: Hypoalbuminemia, cholecystectomy, cholelithiasis, difficult cholecystectomy.

Introduction

Cholelithiasis is one of the most common pathologies of the digestive tract, its incidence is affected by factors such as ethnicity, gender (more frequent in women), a high-fat diet, pregnancy, obesity, among others.[1-3] In Western societies, between 10% and 30% of the inhabitants suffer from cholelithiasis and each year there are one million new cases.[1]

In developed countries it is estimated that there are approximately 25 million adults with cholelithiasis, presenting a total of 800,000 new cases per year. An estimated 10-20% of Americans have gallstones, and up to one-third of these people will develop acute cholecystitis.[4] In Latin America, it is reported that between 5–15% of the inhabitants have gallstones.[1,5]

At the General Hospital of Matamoros Tamaulipas "Dr. Alfredo Pumarejo Lafaurie", for 2009 the prevalence of cholelithiasis in those under 18 years of age was 3.6%.[6]

In 2007, 218,490 consultations for cholecystitis were granted, occupying the first place as a cause of consultation in General Surgery, with a prevalence of 5 to 20%.[1,4]

Cholecystectomy is the most frequently performed surgical intervention in this department, after cesarean section, cholecystectomy is the second most frequently performed surgical intervention at the Mexican Social Security Institute (IMSS), with a total of 69,675 cholecystectomies of which 22,528 were performed by laparoscopy.[4]

Recent studies have revealed that chronic inflammation is closely associated with increased cytokine production. Among several types of inflammatory cytokines, interleukin-6 (IL-6) is well known to be a multifunctional cytokine that acts on a variety of cells, including immunocompetent cells and hematopoietic cells, to trigger proliferation and differentiation.[7,8] From a clinical point of view, it is important to take into account that IL-6 stimulates hepatocytes to produce acute-phase proteins, including C-reactive protein (CRP) and IL-6, which decreases the level of serum albumin synthesis.[9,10]

From the Department of General Surgery at Hospital General 450, Durango, Mexico. Received on October 9, 2020. Accepted on October 14, 2020. Published on October 15, 2020.

DOI 10.17605/OSF.IO/VXH8A

Similarly, IL-6 causes both the proliferation of neutrophils and the differentiation of megakaryocytes to platelets, phenomena that are related to the underlying mechanisms of chronic inflammation.[11]
In the Surgery Service of the General Hospital 450, we have observed greater surgical difficulty in patients with hypoalbuminemia, when they undergo laparoscopic cholecystectomy.

Cholecystectomy with a laparoscopic approach is the treatment of choice for gallbladder pathologies. It is the most frequently performed minimal access surgery in the world.[1-3]

Although laparoscopic cholecystectomy is full of details, the exposure and dissection of the elements included in the cholecystohepatic triangle assumes particular interest and is probably the surgical step that generates the greatest stress on the surgeon, given the great possibility of incurring an injury on the bile duct. Before starting any dissection maneuver, it is important to take advantage of the force of gravity to achieve the greatest possible exposure during surgery; in this case, an inverted Trendelenburg position (between 15 and 20 ° is necessary) and lateral rotation to the left of the surgical table approximately 15 ° will give us the best exposure of the subhepatic space.

There are five high-security maneuvers for laparoscopic cholecystectomy 1) Retraction of the fundus of the gallbladder at 12 o'clock, 2) Retraction of Hartmann's bag at 7 o'clock, 3) Identify what appears to be the cystic duct, 4) identify what appears to be the cystic artery, 5) Verify that no duct returns to the liver. To gain a better understanding of these maneuvers, it is necessary to take as a point reference the center of the cholecystohepatic triangle in the laparoscopic vision and hence imagine "radio" in the manner of the hands of a clock.[12]

Difficult laparoscopic cholecystectomy refers to the surgical removal of the gallbladder when there are some associated conditions of the same organ or its neighboring organs or the patient, which do not allow an easy, fast and comfortable dissection of the gallbladder, and which result in prolongation of surgical time and an increased risk of complications for the patient.[12]

There are multiple and different types of risk factors that could predict which patients will have difficulties when performing a cholecystectomy; the best known are the male sex, the elderly (age over 65 years), obesity, diabetes mellitus, acute cholecystitis, and previous abdominal surgery.[13]

Others, no less important, are a long history of gallbladder disease, leukocytosis and systemic signs of sepsis; also, ultrasound findings of the thickened gallbladder wall, perivesicular fluid, calcified or scleroatrophic gallbladder, large or compacted stones in Hartmann's bag, and bile duct dilation.[14]

There may be other situations that could make a cholecystectomy very difficult, such as very large liver, anatomical alterations, liver cirrhosis, cholecystoenteric fistulas, gallbladder cancer.[15]

Difficult laparoscopic cholecystectomy is a problem that any surgeon could face. There are different definitions, but the conversion rate and iatrogenic lesions are frequently considered indicators of a difficult laparoscopic cholecystectomy. Predicting difficult laparoscopic cholecystectomy can help the surgeon prepare for intraoperative challenges, optimize surgical planning, and improve patient counseling.[16]

Difficult laparoscopic cholecystectomy is defined as that procedure that required > 60 minutes of total operative time associated with technical difficulties or complications (bleeding), a conversion necessary to complete the procedure.[17]

Tapia Jurado et al. comment that the assessment of nutritional status is essential in the surgical patient, since the metabolic and neuroendocrine response to surgical trauma or the underlying disease of these patients lead to an increase in nutrient demands, in addition to the fact that their contribution is generally difficult. In this way, those subjects who are malnourished have a higher risk of presenting complications when they undergo elective or emergent surgery.

The clinical subjective global evaluation alone, or combined with simple biochemical parameters, such as serum albumin, could represent a fundamental tool due to its speed and low cost to detect those surgical patients at risk of presenting complications.[14]

Albumin is the protein that causes 80% of oncotic pressure in plasma. Also, it has other characteristics, based on its molecular structure, that can be considered important when talking about the critical patient: A healthy human of approximately 70 kg produces up to 14 g of albumin per day. This means that the hepatic synthesis of albumin consists of approximately 200 mg/kg of body weight/day, to allow a serum range of 35-45 g/L and total body content of approximately 300 g of albumin. Albumin has a half-life of approximately 21 days, considering a daily degradation rate of 4%. After being synthesized in the liver from amino acids derived from protein muscle catabolism or intestinal absorption, albumin is secreted into the bloodstream (the liver does not store it) and is distributed to all tissues in the body. As albumin is distributed in the hepatic interstitial space, It is important to consider that the concentration of colloids in this space is probably an osmotic regulator for hepatic albumin synthesis, possibly the main one in the absence of stressful conditions. Albumin synthesis is decreased by cytokines such as interleukin-1 (IL-1)[10]

DOI 10.17605/OSF.IO/VXH8A

and 6 (IL-6) and tumor necrosis factor-a (TNFa). Insulin is required for proper synthesis, where as corticosteroids have a dual effect: they increase the synthesis of albumin in combination with insulin or amino acids, but they also increase the catabolism of albumin.[18]

Hypoalbuminemia in adults is defined by a decrease in intravascular albumin level <3.5 g / dL. Potential mechanisms for hypoalbuminemia include decreased synthesis (liver disease, protein malnutrition), increased tissue catabolism (sepsis), kidney loss (nephrotic syndrome), gastrointestinal loss (protein-losing enteropathy), or change in distribution (sequestration). Hypoalbuminemia is a well-known risk factor for mortality and other poor outcomes in various clinical settings, including wellness promotion, acute hospitalizations, end-stage renal disease (ESRD), and decompensated heart failure.

In surgical patients, hypoalbuminemia has been shown to be related to the need for reoperation, prolonged hospital stay, wound complications, renal failure, gastrointestinal dysfunction, and increased mortality.[18]

Ishizuka M, et al, conducted a study whose objective was to search for risk factors for conversion to open cholecystectomy in patients undergoing elective laparoscopic cholecystectomy for cholecystolithiasis. It was concluded that preoperative hypoalbuminemia is the most important risk factor for conversion to open cholecystectomy: albumin (<3.6 g / dL) (odds ratio, 0.329; 95% CI [0.127-0.850]; P = 0.022.[12]

Lipman JM. et al. in a multivariate analysis of the clinical characteristics in 1421 patients who underwent laparoscopic cholecystectomy, found the following predictive factors for conversion to open cholecystectomy: Male sex: OR 4.06 95% CI [2.42-6.82], leukocytosis: OR 3.01, 95% CI [1.77-5.13]. [13] Low albumin: OR 2.90, 95% CI [1.70-4.96], perivesicular fluid by ultrasound: OR 2.36, [95% CI 1.25-4.47], Diabetes mellistus: OR 1.87 95% CI [1.03-3.42], and hyperbilirubinemia OR 1.8, 95% CI [1.01-3.39].[13]

Simopoulos C et al [17] in a study conducted from 2992 to 2004 in 1804 patients found that the significant predictors of conversion to open cholecystectomy were age> 60 years (OR, 4.74; 95% CI, 2.08–0.67; P <0.001), severity of inflammation (0.07; 95% CI, 4.49–11.14; p <0.001), and previous abdominal surgery (OR, 3.36; 95% CI, 1.49–7.57; P = 0.003).[17]

Methods

Using keywords related to the topic, a systematic review of the literature was carried out, the sample size of 500 patients who underwent laparoscopic cholecystectomy was determined, and the laparoscopy Department of General Hospital 450, Durango, was visited.

With exclusion criteria, patients who do not have a registry of liver function tests in the clinical record, or patients who presented anatomical variants and previous supraumbilical surgeries in the abdomen. A list of 692 patients was obtained from 2012 to 2019, subsequently, the clinical record of each patient was obtained, and their variables were recorded, it was carried out. Sociodemographic variables, chronic degenerative diseases, pre-surgical laboratories were evaluated, with interest in the "serum albumin level", as well as "surgical time", "bleeding", "adhesions", "postoperative complications", use of "drains", use of intraoperative "antibiotic therapy", "conversion to open surgery", "gallbladder difficult", "difficult laparoscopic cholecystectomy" and "gallbladder wall thickness". A descriptive analysis of all variables was carried out. The categorical variables with absolute frequency (N) and relative frequency (%). The numerical variables with measures of central tendency (mean and median) and dispersion (standard deviation), to associate categorical variables, the *Pearson X^2 test* was used, with their respective *Yates and Fisher* corrections in 2x2 tables. To quantify the risk factors, the Odds Ratio was used with their respective 95% confidence intervals.

Results

A total of 692 clinical records were reviewed, according to sex, there was a female predominance in 86.4%, regarding the age of the patients in general, the average age of 40.5 years is shown, with the minimum age being female 12 years.

Regarding the weight in our patients, an average of 82.34 kg is observed in the male sex, with a range of 54 kg to 143 kg, concerning the female sex an average of 74.28 kg is presented with a range of 39 kg to 181 kg. The presence of chronic degenerative diseases was 20.9%, with arterial hypertension the most frequent with 68.2%.

Regarding the ultrasound before surgery, 54% of the men reported a thickened wall, considering it greater than 3 mm, in our analysis we did not find a statistically significant association between the ultrasound report and the difficult gallbladder.

We consider the presence of pyocholecyst, hydrocholecyst, acute or subacute inflammation, gangrenous or scleroatrophy, as a difficult gallbladder, defining difficult laparoscopic cholecystectomy (DLC), as a procedure that required more than 120 minutes of total surgery or more. 40 min to achieve

DOI 10.17605/OSF.IO/VXH8A

Supervisory Variable	Associated variables	Square chi	P-value	Odds Ratio	$IC_{95\%}$ Lower Limit	$IC_{95\%}$ Upper Limit
Hypoalbuminemia	Difficult Gallbladder	10.69	0.001	2.232	1.36	3.64
	Bleeding	6.22	0.013	2.54	1.193	5.41
	Use of antibiotic	5.87	0.015	3.57	1.19	10.72
	Drains	4.12	0.042	1.72	1.01	2.92
	Prolonged Surgical time	9.03	0.003	2.06	1.2	3.33
	Conversion to open surgery	20.68	0.000	8.1	6.64	9.89

Table 1. Association of hypoalbuminemia with determinants of difficult laparoscopic cholecystectomy

critical safety view, it was associated with technical difficulties or complications, as well as placement of drains, or conversion rate to open surgery.

A total of 241 DLC were considered with an association to the female sex of 32.6% (Chi^2 = 9.54 p-value = 0.002 OR = 1.98 M / F 95% CI [1.27 - 3.07]), as well as a conversion rate of 0.4% with association to hypoalbuminemia Chi^2 = 20.68 p-value = 0.000 OR = 8.10 95% CI [6.6 - 9.8].

Hypoalbuminemia is a risk factor for difficult laparoscopic cholecystectomy: Chi^2 = 6.1 p-value = 0.013 OR = 1.76 95% CI [1.1 - 2.7].

The prevalence of hypoalbuminemia in postoperative laparoscopic cholecystectomy patients in the General Surgery Service from 2012 to 2019 is 12.7%.

Hypoalbuminemia is related to an increase in the conversion rate to open surgery Chi^2 = 20.68 p-value = 0.000 OR = 8.10 95% CI [6.6 - 9.8] **(table 1)**

Discussion

Laparoscopic cholecystectomy is the most frequently performed surgery in the world for gallstones. In the General Hospital 450, which is a second-level hospital and reference center for the non-eligible population of the state of Durango and neighboring states such as Zacatecas and Coahuila, more than 750 surgeries of this type are performed per year, which is a higher number to those carried out in the Central Military Hospital.[27]

As reported in the literature in our population, cholelithiasis is a predominant pathology of the female sex (86%), with a 4:1 ratio to the male sex and the average age is in the same 40 ± 15 years to what is reported in the IMSS Clinical Practice Guide.[1]

Difficult laparoscopic cholecystectomy refers to the surgical removal of the gallbladder when there are some associated conditions of the same organ or its neighboring organs or the patient, which do not allow an easy, fast and comfortable dissection of the gallbladder, this translates into prolongation of the gallbladder. surgical time and increased risk of complications for the patient. In our study, the prevalence of difficult laparoscopic cholecystectomy from 2012 to 2019 was 34.8%, taking into account the presence of a difficult gallbladder, intraoperative bleeding greater than 50 ml, intraoperative antibiotic administration, placement of a drain (Penrose type), longer surgical time 60 minutes and conversion to open surgery.

Cholecystectomy in men is of greater risk than in women, because it is related to a greater number of urgent surgeries, it presents clinically with greater severity, surgical treatment is delayed, which triggers a greater number of complicated patients with more technical difficulties at the time of surgery, therefore, increase morbidity.[28] In our study, only scheduled surgery patients were included and the prevalence of difficult surgery in males was 48.9% with a risk up to three times higher than in females.

Albumin synthesis is affected by nutritional status and disease, hormones such as insulin, thyroxine, and cortisol stimulate albumin synthesis. It has several key physiological functions, it is the main protein for maintaining oncotic pressure, besides, it acts as a transporter for fatty acids, bile acids, colesterol, and medications.

Hypoalbuminemia in adults is defined by a decrease in intravascular albumin level <3.6 g / dL. Potential mechanisms for the presence of hypoalbuminemia include decreased synthesis (liver disease, protein malnutrition), increased tissue catabolism (sepsis), kidney loss (nephrotic syndrome), gastrointestinal loss (protein-losing enteropathy), or change in distribution (kidnapping). Hypoalbuminemia is a well-known risk factor for mortality in addition to being related to the need for re-operation, prolonged hospital stay, wound complications, kidney failure, gastrointestinal dysfunction, etc.

Recent studies have indicated that chronic inflammation is closely associated with hypercytokinemia such as IL-6 which is well known to act on a wide variety of cells including autoimmune and hematopoietic cells as a trigger for proliferation and differentiation. From the clinical point of view, it is important to consider IL-6 as a stimulant of hepatocytes to produce acute-phase proteins such as

DOI 10.17605/OSF.IO/VXH8A

C-reactive protein (CRP), thus decreasing the synthesis of albumin.[12]

In our study, an association of hypoalbuminemia was found with the presentation of difficult laparoscopic cholecystectomy Chi^2 = 6.1 p-value = 0.013 with an OR = 1.76 95% CI [1.1 - 2.7] as well as with the presence of a difficult gallbladder (hydrocholecyst, pyocolecyst, cholecystitis acute, subacute), intraoperative bleeding, need for intraoperative antibiotic administration, increased need for the placement of a Penrose drain, longer surgical time and conversion to open cholecystectomy.

Conclusion

Cholelithiasis is one of the most common digestive tract pathologies. Cholecystectomy is one of the most performed abdominal surgical procedures, and in developed countries, many are performed laparoscopically. As an example, 90% of cholecystecytomies in the United States are performed laparoscopically. Laparoscopic cholecystectomy is considered the "gold standard" for the surgical treatment of gallstone disease.

This procedure results in less postoperative pain, better esthetics, and shorter hospital stays, and occupational disability than open cholecystectomy. Therefore, the adequate protocolization of patients who will undergo laparoscopic cholecystectomy is crucial, albumin plays an important role as a predictor factor for difficult laparoscopic cholecystectomy, with levels below 3.6 mg/dL.

The prevalence of hypoalbuminemia in postoperative laparoscopic cholecystectomy patients in our service is 12.7%.

Hypoalbuminemia is related to an increase in the conversion rate to open surgery, therefore it is important to pay attention to serum albumin levels.

In our study, we observed that an adequate classification of cholecystitis is necessary, A large number of cholecystitis rating scales have been developed in the past, which aim to predict both intraoperative and postoperative outcomes; however, few of these scales take intraoperative anatomical differences into account; however, prospective studies are required to validate these classifications.

Conflicts of interests

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Acknowledgements

Thanks to Dr. Armando Melero Vela, for his patience, his good humor, and his support. Expert in the subject that this article deals with, for being at my disposal to solve all the doubts that have arisen along the way.

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 DOI 10.17605/OSF.IO/VXH8A