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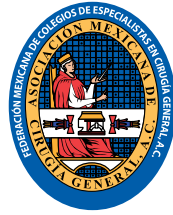
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Does obesity influence morbidity and mortality in laparoscopic cholecystectomy?

¿Influye la obesidad en la morbimortalidad de la colecistectomía laparoscópica?

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Keywords:

laparoscopic cholecystectomy, obesity, complications.

Palabras clave:

colecistectomía laparoscópica, obesidad, complicaciones.

ABSTRACT

Introduction and objective: cholecystectomy is the treatment of choice for gallbladder lithiasis, which is not free of complications (2-5%) related to mastery of the technique, inflammation of Calot's triangle, or anatomical variants. Recently, obesity has been considered a risk factor, so we decided to carry out the present study in two hospitals in southeastern Mexico. **Material and methods:** a prospective, multicenter, comparative study in patients submitted to laparoscopic cholecystectomy by surgeons with more than 15 years of experience, classified into three groups: A) normal weight, B) overweight, and C) obesity. Variables analyzed: anthropometric characteristics, comorbidities, surgical time, days/stay, complications, and mortality. Statistical analysis: the results were analyzed by descriptive and inferential statistics with the SPSS 24.0 program. **Results:** 317 patients underwent laparoscopic cholecystectomy. Group A: 134 cases, mean age 45.78 ± 14.6 years, women 83.58%, body mass index (BMI) 22.6 ± 4.56 kg/m², comorbidities 17.16%, surgical time 54.07 ± 14.10 minutes, days/stay 1.96 ± 2.23, no complications or deaths. Group B: 89 patients, mean age 51.26 ± 13.23 years, female sex 85.39%, BMI 28.6 ± 4.50 kg/m², comorbidities 23.59%, surgical time 56.72 ± 9.17 minutes, days/stay 1.89 ± 3.4, complications 3.68%, no mortality. Group C: 94 patients, mean age 58.5 ± 9.8 years, female sex 77.78%, BMI 32.50 ± 6.87 kg/m², surgical time 63.16 ± 12.4 minutes, days/stay 2.84 ± 3.42, complications 10.63%, no death (p = 0.0001). **Conclusions:** in our study, the highest number and severity of complications occurred in patients with BMI > 34 kg/m², so obesity should be considered in patients undergoing laparoscopic cholecystectomy. However, a more significant number of cases is required to confirm this hypothesis.

RESUMEN

Introducción y objetivo: la colecistectomía es el tratamiento de elección de la litiasis vesicular, la cual no está exenta de complicaciones (2-5%) relacionadas con dominio de la técnica, inflamación del triángulo de Calot o variantes anatómicas. Recientemente se ha considerado la obesidad como un factor de riesgo, por lo que decidimos realizar el presente estudio en dos hospitales del sureste de México. **Material y métodos:** estudio prospectivo, multicéntrico, comparativo en pacientes sometidos a colecistectomía laparoscópica por cirujanos con más de 15 años de experiencia, clasificados en tres grupos: a) peso normal, b) sobrepeso y c) obesidad. Variables analizadas: características antropométricas, comorbilidades, tiempo quirúrgico, días/estancia, complicaciones y mortalidad. Análisis estadístico: los resultados fueron analizados mediante estadística descriptiva e inferencial, con el programa SPSS 24.0. **Resultados:** fueron sometidos a colecistectomía laparoscópica 317 pacientes. Grupo A: 134 casos, edad promedio 45.78 ± 14.6 años, mujeres 83.58%, índice de masa corporal (IMC) 22.6 ± 4.56 kg/m², comorbilidades 17.16%, tiempo quirúrgico 54.07 ± 14.10 minutos, días/estancia 1.96 ± 2.23, sin complicaciones ni defunciones. Grupo B: 89 pacientes, edad promedio 51.26 ± 13.23 años, sexo femenino 85.39%, IMC 28.6 ± 4.50 kg/m², comorbilidades 23.59%, tiempo quirúrgico 56.72 ± 9.17 minutos, días/estancia 1.89 ± 3.4, complicaciones 3.68%, sin mortalidad. Grupo C: 94 pacientes, edad promedio 58.5 ± 9.8 años, sexo femenino 77.78%, IMC 32.50 ± 6.87 kg/m², tiempo quirúrgico 63.16 ± 12.4 minutos, días/estancia 2.84 ± 3.42, complicaciones 10.63%, ninguna defunción. (p = 0.0001). **Conclusiones:** en nuestro estudio el mayor número y gravedad de las complicaciones se presentaron en pacientes con IMC > 34 kg/m², por lo que la obesidad debe considerarse en enfermos que serán sometidos a colecistectomía laparoscópica. Sin embargo, se requiere mayor número de casos para confirmar esta hipótesis.

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INTRODUCTION

Laparoscopic cholecystectomy is currently the best therapeutic resource for gallbladder stone disease. In recent decades, this technique has increased due to its safety and advantages.^{1,2} It is also one of the most frequently performed surgical procedures in general hospitals worldwide; in the United States alone, in 2014, 750,000 cholecystectomies were performed.³⁻⁷

In the last three decades, lifestyle modifications in our population, consisting of excessive food consumption and a sedentary lifestyle, have led to an increase in body mass index (BMI),⁸⁻¹¹ and our country has not escaped this trend: as of 2014, obesity is occupying the second place worldwide.¹²⁻¹⁵ This means that a large number of patients with obesity will require a surgical solution for gallbladder lithiasis disease.

Recently, publications have appeared that point to obesity as an additional risk factor for the presentation of complications of the laparoscopic procedure,¹²⁻¹⁶ so we decided to conduct a study to determine whether obesity influences morbidity and mortality in patients undergoing laparoscopic cholecystectomy.

MATERIAL AND METHODS

Type of study: prospective, multicenter, observational, and comparative. **Study universe:** consecutive patients submitted to laparoscopic cholecystectomy in two hospitals in the city of Veracruz, one of the public system (*Hospital Naval de la Secretaría de Marina*) and the other of private care (*Hospital Español de Veracruz*), during the period from January 2017 to December 2019. Patients were classified into three groups, according to the World Health Organization (WHO) Criteria for classifying obesity, taking into account the weight range and body mass index (BMI); group A: patients with normal weight (BMI 18.5 and 24.9 kg/m²); group B: patients with overweight BMI (25 and 29.9 kg/m²); and group C: patients with obesity (BMI 30 or more kg/m²). This last group, in turn, was subdivided into: type I obesity (BMI 30-34.9 kg/m²), type II obesity (BMI 35-39.9 kg/m²), type III obesity (BMI 40-49.9 kg/m²) and type IV obesity (BMI ≥ 50 kg/m²). **Variables**

analyzed: age, sex, BMI, risk factors, surgical time, average days/hospital stay, postoperative complications, and mortality. **Statistical analysis:** absolute and relative frequencies were used to describe nominal variables, and mean, and standard deviation were used for their distribution. SPSS version 25.0 statistical software (SPSS, Inc, Chicago, ILL) was used.

RESULTS

During the period studied, 317 patients underwent laparoscopic cholecystectomy; the average age of the entire group was 45.78 ± 13.28 years (range 12-87 years); of these, 192 cases (84.21%) were female, and 36 (15.79%) were male; the BMI was 32.87 ± 6.02 kg/m² (range 18-44 kg/m²).

Group A, patients with normal weight: was composed of 134 cases (42.28%), with an average age of 45.78 ± 14.6 (range 12-87), 112 (83.58%) female and 22 (16.42%) male, with average BMI of 22.6 ± 4.56 kg/m² (range 18.5-24). The anthropometric characteristics of this group compared with those with overweight or obesity were not statistically significant, except that most cases corresponded to the female sex (p = 0.001), as in the overweight and obesity groups. In this group, 23 (17.16%) patients had associated comorbidity: arterial hypertension in 15 (11.19) cases, diabetes mellitus in five (3.73%), asthma in two (1.49%) and cirrhosis in one (0.75%) (*Table 1*). The mean operative time was 54.07 ± 14.10 minutes (range 35-120), and the mean days/hospital stay was 1.96 ± 2.23 days (range 1-3). No postoperative complications were reported or deaths (*Table 2*).

Group B, overweight cases: consisted of 89 (39.03%) patients, with a mean age of 51.26 ± 13.23 years (range 21-78), female sex predominated with 76 (85.39%) cases, over male sex with 13 (14.61%) cases; mean BMI was 28.6 ± 4.50 kg/m² (range 18-29). The anthropometric characteristics did not show statistically significant differences compared to the normal weight group, except in the distribution by sex, since the female was predominant (p = 0.001). This group presented comorbidity in 21 (23.59%) cases: arterial hypertension in 17 (19.10%), diabetes mellitus

Table 1: Demography and risk factors of the population studied.

Parameter	Normal weight n (%)	Overweight n (%)	Obesity n (%)	p
Population	134 (42.28)	89 (39.03)	94 (41.23)	
Demography				
Average age years [range]	45.78 ± 14.6 [12-87]	51.26 ± 13.23 [21-78]	58.5 ± 9.87 [28-78]	0.679
Sex				
Female	112 (83.58)	76 (85.39)	74 (77.78)	
Male	22 (16.42)	13 (14.61)	20 (22.28)	0.001
Risk factors				
Associated comorbidities	23 (17.16)	21 (23.59)	44 (46.81)	0.065
Diabetes mellitus	5 (3.73)	17 (19.10)	10 (10.64)	
High blood pressure	15 (11.19)	3 (3.37)	32 (34.04)	
Asthma	2 (1.49)	0	2 (2.13)	
Cirrhosis	1 (0.75)	0	0	
Venous insufficiency	0	1 (1.12)	0	

Table 2: Results of surgical intervention and morbidity and mortality in the groups studied.

Parameter	Normal weight n (%)	Overweight n (%)	Obesity n (%)	p
Population	134 (42.28)	89 (39.03)	94 (41.23)	
Surgical procedure results				
Surgical time [min] [range]	54.07 ± 14.10 [35-120]	56.72 ± 9.17 [37-120]	63.16 ± 12.4 [45-150]	0.235
Average days/stay [range]	1.96 ± 2.23 [1-3]	1.89 ± 3.4 [1-3]	2.84 ± 3.42 [3-21]	0.429
Complications	0	1 (3.68)	10 (10.63)	0.005
Wound infection	0	1 (1.31)	6 (6.38)	
Biloma	0	0	2 (2.13)	
Port hernia	0	0	1 (1.06)	
Biliary fistula	0	0	1 (1.06)	
Mortality	0	0	0	

in three (3.37%), and deep venous insufficiency in the lower extremities in one (1.12%) (Table 1). The mean operative time was 56.72 ± 9.17 minutes (range 37-120). The mean days/stay was 1.89 ± 3.4 days (range 1-3). Only one case (1.31%) presented epigastric port wound infection; there were no significant complications or mortality (Table 2).

Group C, obese patients: 94 patients (41.23%), the average age of the group was 58.5 ± 9.87 years (range 28-78), the predominant sex was female with 74 (77.72%) cases, over male with 20 (22.28%) cases. The mean BMI was 32.50 ± 6.87 kg/m² (range 30-40). The risk factors found were: arterial hypertension in 32 (34.04%) cases, diabetes mellitus in 10 (10.64%), and asthma in two (2.13%) (Table 1). The mean operative time was 63.16 ± 12.4 minutes (range 45-150), and the mean days/stay was 2.84 ± 3.42 days (range 3-21). In this group, ten complications (10.63%) were reported ($p = 0.005$), which were: surgical wound infection in six (6.38%) cases, biloma in two (2.13%), epigastric port hernia in one (1.06%) case and external biliary fistula in another (1.06%), which corresponded to a patient with grade III obesity with acute cholecystitis, who underwent subtotal cholecystectomy with drainage of the subhepatic space and required hospitalization for 21 days. The three major complications were resolved satisfactorily, and there was no death.

DISCUSSION

Laparoscopic cholecystectomy is the best treatment option for gallbladder stone disease with a perioperative complication rate that ranges from 2 to 5%, of which 3 to 15% are usually severe and are associated with a mortality rate of 0.7 to 1.5%; they usually occur in elderly patients with associated comorbidities, and in immunocompromised patients.^{1,17-19} Postoperative complications have been attributed to the learning curve of the laparoscopic technique, the surgeon's inexperience, inadequate patient selection and, recently, also to the degree of obesity.²⁰⁻²⁴

At the Hospital General "Dr. Gaudencio Gonzalez" in Mexico,¹⁹ when evaluating post-

laparoscopic cholecystectomy complications, Ramirez observed that they occurred more frequently in women with an average age of 47.8 years and BMI over 24.8 kg/m². Similar results obtained by Hussien at the Walles Hospital in Belfast, New Ireland,²⁴ Banz at the University of Bern in Switzerland⁵ and Aziz at the University of Arizona in the United States of America,²⁵ corroborate that the greater the degree of obesity the greater the number of complications; also pointing out that, although the disease is more frequent in women, the most significant complications usually occur in men;²⁶⁻²⁹ recommending that in such severe cases, subtotal cholecystectomy can be performed to avoid injury to the biliary tract.³⁰⁻³³

The results of our study confirm what is reported in the world literature, cholelithiasis was more frequent in the female sex (84.21%) than in the male sex (15.79%) ($p = 0.001$), with an average age for the whole group of 45.78 ± 13.28 years and BMI of 32.87 ± 6.02 kg/m².

Although 28.29% had associated comorbidity (arterial hypertension, type 2 diabetes, asthma, cirrhosis, and deep venous insufficiency in the lower extremities), this did not constitute a significant risk factor in the surgery results.

The surgical time employed in patients with normal weight and overweight was similar (55.84 ± 8.23 minutes), and in cases with obesity, it was slightly higher (63.16 ± 12.4). However, there was no statistical significance between the three groups ($p = 0.235$).

As can be seen in Table 2, the highest number of complications occurred in patients with obesity, compared to the normal weight or overweight group, with statistical significance ($p = 0.005$). The most severe complications (biloma and biliary fistula) occurred in patients with grade II and III obesity, which fortunately were satisfactorily resolved with conservative management.^{17,25}

The mean days/stay was 1.91 ± 3.37 days in the first two groups and 2.84 ± 3.42 in the obese patients, but without a significant statistical difference ($p = 0.429$). However, one of the male patients with type III obesity, who underwent subtotal cholecystectomy, presented the most severe complications and remained

hospitalized for 21 days, requiring support from the Intensive Care Unit.

CONCLUSIONS

Our study shows the results of the experience in managing gallbladder stones in a population of southeastern Mexico. The learning curve was eliminated since the participating surgeons in the two institutions had more than ten years of experience performing laparoscopic cholecystectomy. Although the cohort of cases is small, it allows us to conclude that the most severe complications occur in patients with grade II and III obesity, so it should be considered a risk factor, especially for incidental lesions of the biliary tract.

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according to the protocols established in our work center, we declare that we have followed the protocols for the privacy of patient data, preserving their anonymity.

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Role of Nrf2 and oxidative stress in the progression of non-alcoholic steatohepatitis to hepatocarcinoma

Papel de Nrf2 y estrés oxidativo en la progresión de esteatohepatitis no alcohólica a hepatocarcinoma

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Palabras clave:

Nrf2, radicales libres, estrés oxidativo, esteatohepatitis no alcohólica, cirrosis hepática, hepatocarcinoma.

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ABSTRACT

Oxidative stress and oxidation-reduction reactions are present in all biological processes. In patients with metabolic syndrome, they contribute to the development of non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma, through processes of lipotoxicity, cytokine recruitment, stellate cell activation, progressive collagen synthesis, DAMPs (injury-associated molecular pattern), PAMPs (pathogen-associated molecular pattern) and irreversible damage to mitochondrial DNA. Nrf2 is the most important transcription factor in the regulation of enzymatic antioxidant response gene expression and plays a major role in the cytoprotective response to acute inflammation and liver regeneration. However, it has also been associated with the development of chemoresistance and tumor recurrence. In this article, we review the existing evidence in this regard.

RESUMEN

El estrés oxidativo y las reacciones de óxido-reducción se encuentran presentes en todos los procesos biológicos. En pacientes con síndrome metabólico, contribuyen al desarrollo de esteatohepatitis no alcohólica, cirrosis y carcinoma hepatocelular, mediante procesos de lipotoxicidad, reclutamiento de citocinas, activación de células estelares, síntesis progresiva de colágena, DAMPs (patrón molecular asociado a lesiones), PAMPs (patrón molecular asociado a patógenos) y daño irreversible al ADN mitocondrial. Nrf2 es el factor de transcripción más importante en la regulación de la expresión de los genes de la respuesta antioxidante enzimática y juega un papel primordial en la respuesta citoprotectora ante la inflamación aguda y en la regeneración hepática. Sin embargo, se ha asociado también al desarrollo de quimiorresistencia y recurrencia tumoral. En este artículo, hacemos una revisión sobre la evidencia existente al respecto.

OXIDATION AND REDUCTION REACTIONS AND THEIR RELATIONSHIP TO LIVER DISEASE

Oxidation and reduction (redox) reactions are present in almost every biological process. The interactions between endogenous and exogenous oxidants and antioxidant systems, both enzymatic and non-enzymatic, have fundamental pathophysiological implications, from acid-base balance, bioenergetic processes, oxidation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), as well as their

mutations, to a state of excessive oxidation related to the development of diseases. In aerobic metabolism, these reactions produce free radicals. Free radicals are unstable chemical molecules that have an unpaired electron and are characterized by being highly reactive with other molecules and are by-products of fatty acid metabolism and oxidation in peroxisomes, mitochondria, and smooth endoplasmic reticulum. The most common free radicals are superoxide anion (O_2^-), hydroxyl radical (OH^-), peroxy radical (ROO^-), and alkoxy radical (RO^-), of which the hydroxyl radical is

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the most potent, subtracting a hydrogen atom from the methylene group ($-\text{CH}_2-$) of fatty acids, leaving a free bond on the carbon atom ($-\text{CH}^\cdot$), initiating a chain reaction, taking hydrogenions from the other fatty acid molecules until the substrate is totally consumed or the reaction is stopped by an antioxidant molecule. There are also other free radicals not associated with oxygen^{1,2} (Figure 1).

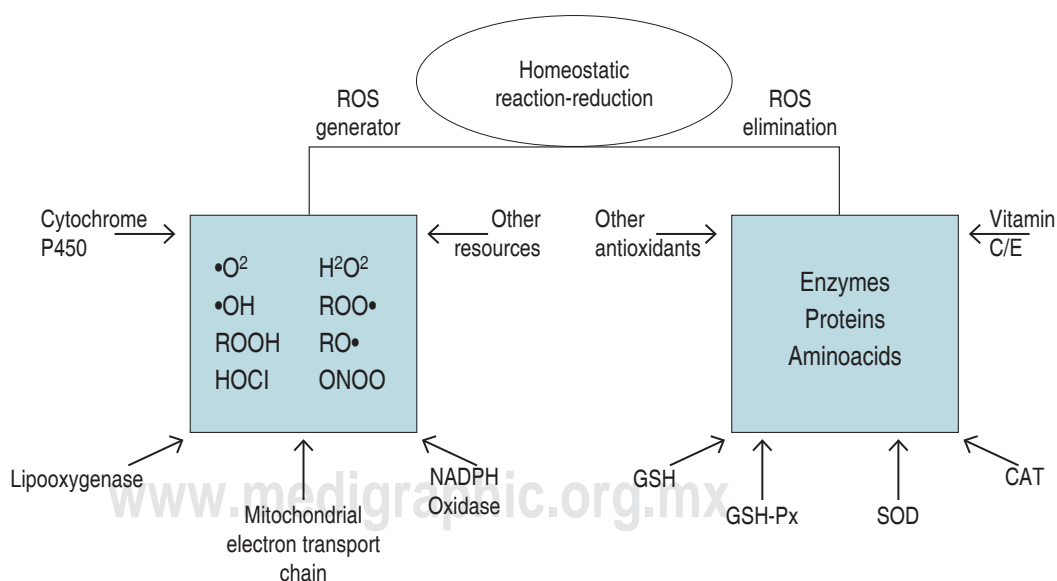
Oxidative stress is defined as the imbalance between the production of oxidative molecules and the synthesis of antioxidant molecules, leading to tissue damage.^{3,4} In patients with non-alcoholic steatohepatitis (NASH), oxidative stress causes hepatocyte dysfunction or death, affecting enzymes involved in lipid metabolism.⁵ Kupffer cells and neutrophils are mainly responsible for the hepatic production of free radicals.⁶

The antioxidant response is regulated by the nuclear factor $\kappa\beta$ ($\text{NF}\kappa\beta$), the transcription factor AP-1, and the nuclear factor erythroid or respiration factor-associated factor (Nrf2) family of factors, of which Nrf2 is the most important regulator of gene expression involved in the enzymatic antioxidant system. Under normal

conditions, Nrf2 is found in the cytoplasm attached to KEAP1, a cytosolic anchoring protein. But during increased oxidative stress Nrf2 detaches from KEAP1 and is translocated to the nucleus, where it activates gene transcription of antioxidant systems, increasing the expression of superoxide dismutase, catalase, glutathione peroxidase 2, glutathione reductase, the thioredoxin, myeloperoxidase, gamma-glutamylcysteine synthetase, and heme oxygenase-1 systems. Hepatocellular Nrf2 activation plays an important role in the cytoprotective response of the liver to oxidative stress. Multiple studies show that hepatocellular Nrf2 concentration is elevated during chronic and persistent oxidative stress processes, acute inflammation, and liver regeneration.^{7,8}

PROINFLAMMATORY STATES AND LIPOTOXICITY-INDUCED FIBROGENESIS IN NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic steatohepatitis is the most frequent liver disease in the world and there



Adapted from: Li S, et al.³⁰

Figure 1: The hemostatic reaction-reduction in the liver.

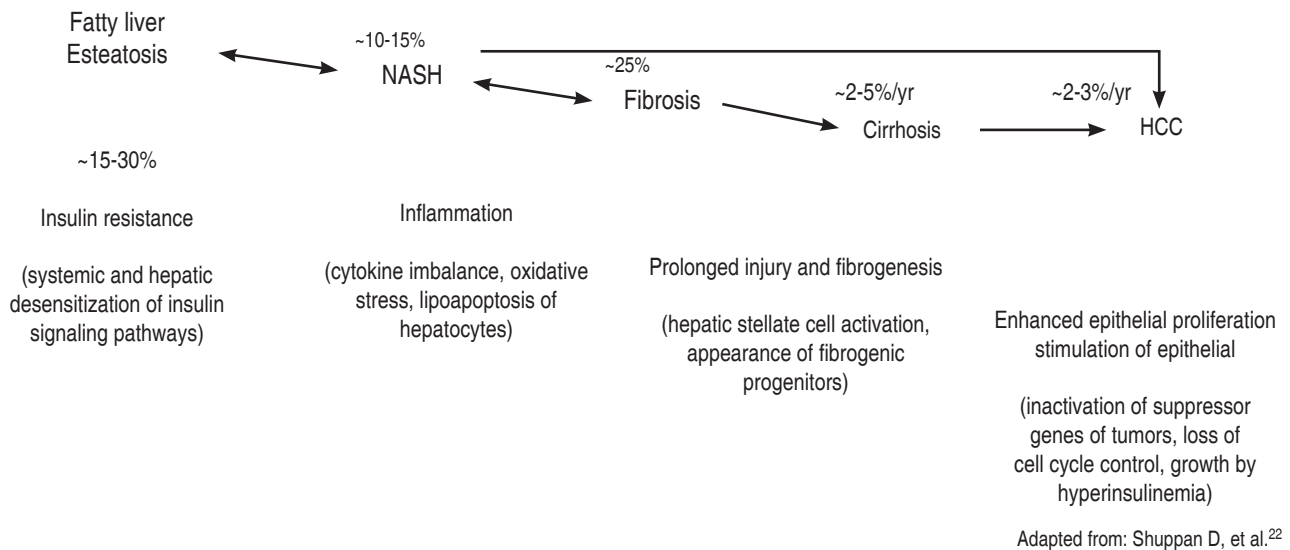


Figure 2: Spectrum of non-alcoholic fatty liver disease. Estimated risks of progression to hepatocellular carcinoma and non-alcoholic steatohepatitis.

HCC = hepatocellular carcinoma. NASH = non-alcoholic steatohepatitis.

is currently a trend in the increase of liver transplantation for cirrhosis.⁹ It increases the spectrum of damage by converting simple hepatic steatosis (NAFL), without evidence of inflammation, into a pattern of progressive fibrosis called steatohepatitis (NASH). It is directly associated with insulin resistance, obesity, diabetes, and dyslipidemia, and is considered the main hepatic manifestation of the metabolic syndrome.^{10,11} It has an overall prevalence of 59.1%¹² by diagnosis through liver biopsy, which increases to 95% in morbidly obese patients.¹³⁻¹⁵ The disease is asymptomatic and slowly progressive, with progression between each degree of fibrosis for every 7.1 years in patients with steatohepatitis and 14.3 in patients with simple steatosis, of which 23% progress to fibrosis and cirrhosis,¹⁶ and up to 7.6% may develop hepatocellular carcinoma¹⁷ (Figure 2). In the Americas, there is a direct correlation between obesity and non-alcoholic fatty liver disease (NAFLD), with a prevalence of 80% in obese patients.¹⁸ A cross-sectional study conducted in 2012 found a prevalence rate of 84.1% of NAFLD diagnosed by ultrasound in patients younger than 60 years with metabolic syndrome¹⁹ (Figure 3).

Non-alcoholic steatohepatitis is the result of the sum of events and risk factors that

begin with the increase in the concentration of free fatty acids in the portal circulation due to the overnutrition of patients with obesity, which produces an increase in triglycerides in hepatocytes and gluconeogenesis. The expansion of adipose tissue increases the production of adipokines, and the synthesis of proinflammatory cytokines such as monocyte chemoattractant protein 1 (MCP1), IL-6, and IL-8, decreases the levels of adiponectin, a counter-regulatory adipokine stimulated by lipid accumulation in adipose tissue and liver, also increases circulating leptin concentrations, promoting fibrogenesis by stimulation of stellate cells. On the other hand, Kupffer cells produce proIL-1 β , IL-12, and TNF- α , which add to the release of lipopolysaccharides (LPS) from the intestinal microbiome and inflammasomes, which are defined as protein complexes that act as sensors and mediators of inflammation related to specific sequence patterns of different pathogens or damage patterns, such as PAMPs and DAMPs. These activate Toll-like receptors-4 (TLR4) in the liver, increasing the synthesis of caspase 1 (Cas1) and thus inducing the maturation of proinflammatory cytokines IL-1 β and IL-8. The production of proinflammatory factors by platelets and Kupffer cells stimulates stellate cells, or Ito cells, in the space of Disse

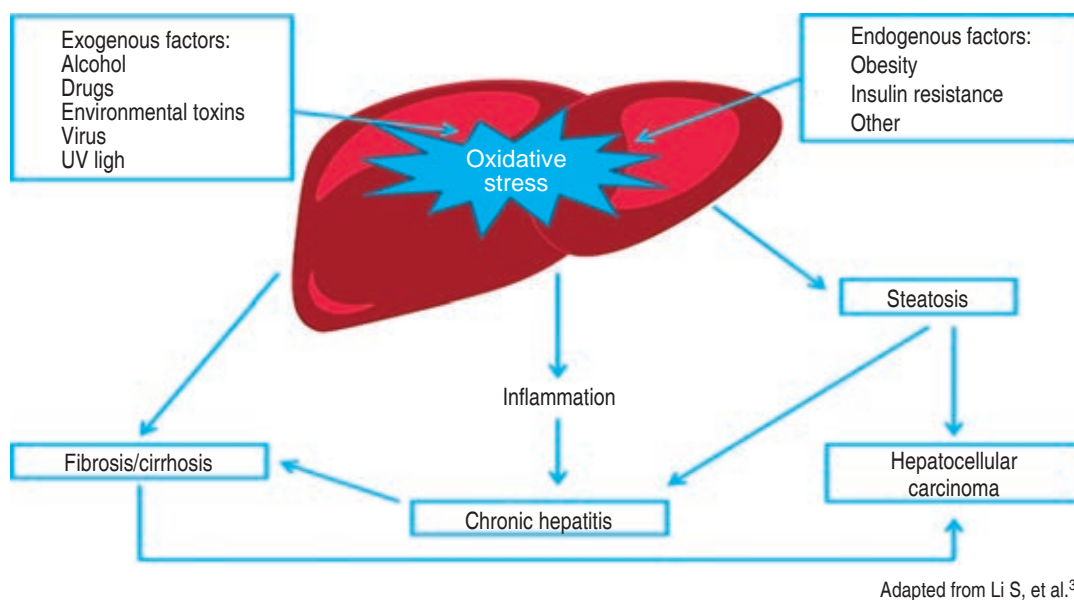


Figure 3: Schematic of general mechanisms of oxidative stress induced by multiple factors in liver disease.

to proliferate and transform into myofibroblasts. Subsequently, the “activated” stellate cells self-stimulate to increase production of TGF- β and TNF- α , paracrine activating adjacent stellate cells, perpetuating fibrogenesis, even when the initial damage has ceased. The result is persistent inflammation, fibrosis, and apoptosis of hepatocytes, mediated by an interrelated process of lipotoxicity, cytokine recruitment, mitochondrial dysfunction, and oxidative stress²⁰ (Figure 4).

OXIDATIVE STRESS AND DNA DAMAGE IN NASH

Oxidative stress also produces epigenetic alterations to mitochondrial and nuclear DNA. Under normal conditions, oxidative damage to nucleosides maintains a balance between DNA oxidation and DNA repair. But under conditions of high oxidative stress, the damage is irreversible, and the tissue concentration of damaged DNA increases. This imbalance has a positive association with the aging process, carcinogenesis, and NASH. The main product of DNA damage due to oxidative stress is 8-hydroxy-deoxy-deoxy-guanosine (8-OHdG), which has been described as an early biomarker of tissue damage. Takahashi et

al.²¹ examined, through immunohistochemistry, hepatocellular oxidative stress in healthy and NASH liver samples. The proportion of hepatocellular 8-OHdG was higher in liver biopsies with NASH than in normal ones (NASH vs. control 64 vs. 37%, respectively, $p < 0.05$). They found no correlation between 8-OHdG expression and histological findings of steatosis, necroinflammation, ballooning, or fibrosis, which translates into the possibility of steatohepatitis, even in biopsies reported as normal; in this study, they also found a positive association between nuclear Nrf2 expression with hepatocellular 8-OHdG levels in NASH patients ($r: 0.65, p < 0.01$).²²

ROLE OF OXIDATIVE STRESS IN THE PATHOPHYSIOLOGY OF NON-ALCOHOLIC STEATOHEPATITIS

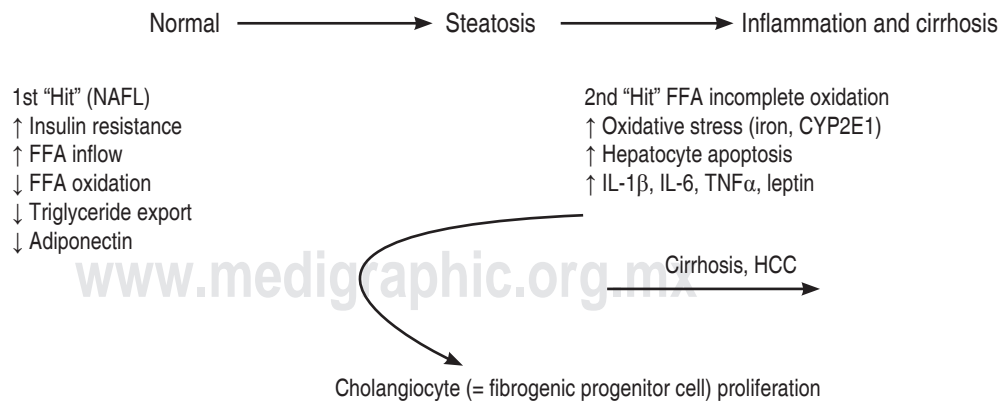
All that is known about the pathophysiology of NASH has allowed the formulation of the “multiple hits” theory, in which dietary, genetic, and epigenetic factors, together with obesity, lead to elevated serum levels of free fatty acids and cholesterol, developing insulin resistance, adipocyte proliferation and changes in the intestinal microbiome. Insulin resistance in tissues

worsens adipocyte dysfunction, induces lipolysis, and promotes the release of adipokines and proinflammatory cytokines such as TNF- α and IL-6; which contributes to the maintenance of the insulin-resistant state. In the liver, increased free fatty acids and changes in the microbiome lead to increased triglyceride synthesis and accumulation, along with mitochondrial dysfunction due to increased oxidative stress and oxygen-free radical production, which promotes hepatic inflammation. Another important related factor is the gut-liver axis. Some studies have shown that the consumption of high-fat diets impairs the intestinal barrier. Increased permeability of the small intestine allows the translocation of molecules that contribute to inflammasome activation and increases endoplasmic reticulum stress.²¹ Fatty liver shows increased susceptibility to lipid peroxidation with increased reactive oxygen species in response, causing mutations in DNA. In addition, some genetic factors play a role in pathogenesis. Variations in proteins such as adiponutrin (PNPLA3) and transmembrane superfamily 2 transmembrane 6 (TM6SF2) have been implicated in alterations in lipid metabolism and increased hepatic steatosis. The liver of patients with obesity is more susceptible to carcinogenesis as a result of impaired ATP production, coupled with a defective apoptosis mechanism and energy

dysregulation and/or hormonal balance, hypoxia, and systemic inflammation.

Both endoplasmic reticulum stress and mitochondrial dysfunction generate apoptosis and fibrosis, processes that lead to the development of hepatic steatosis and NASH. An impaired autophagic function may be a causal factor in the development of hepatocarcinoma in patients with non-alcoholic steatohepatitis. Under normal conditions, it functions as a cell death mechanism and is also an adaptive mechanism to damage. Likewise, autophagy controls the breakdown of lipids contained in hepatocellular deposits; due to this, its deterioration can cause hepatic steatosis and the inability to inhibit the growth of tumor cells.²³

The oxidative stress signaling pathway involves proteins such as *inositol-requiring enzyme 1 α* (IRE1 α), RNA, and endoplasmic reticulum kinases (PKR and PERK, respectively), as well as activated transcription factor 6 α (ATF6 α). When these molecules sense elevated levels of stress in the endoplasmic reticulum, they activate protein-mediated compensatory mechanisms. Stress can trigger the cell death cascade. In addition, chronic stress in the endoplasmic reticulum produces more reactive oxygen species that trigger hepatocyte inflammation through the nuclear factor $\kappa\beta$ (NF- $\kappa\beta$) and Jun-N-terminal kinase (JNK) pathways.^{21,24}



Adapted from: Schuppan D, et al.²²

Figure 4: Pathogenic mechanisms during progression to hepatic steatosis and non-alcoholic steatohepatitis. NAFL = non-alcoholic fatty liver. HCC = hepatocellular carcinoma. FFA = free fatty acids.

DUAL ROLE OF THE KEAP1/NRF2 COMPLEX IN LIVER CARCINOGENESIS

Nrf2 participates in several biological functions, such as metabolism and regulation of the response to xenobiotics, autophagy and apoptosis, pentose synthesis and NADPH generation, maintenance of the Redox balance, lipogenesis, cholesterol synthesis, gluconeogenesis, glycolysis, oxidation, and degradation of fatty acids. It also plays a fundamental role as a cytoprotective transcription factor by activating the cellular antioxidant response, thus being considered the main mechanism for cell survival and tumor suppressor. However, many studies point out that it may promote not only normal cell survival but tumor cells as well, resulting in the progression of neoplastic disease. Hyperactivation of Nrf2 also protects the tumor cell from oxidative stress, chemotherapy, and radiotherapy. Under physiological conditions, the Nrf2 pathway is stimulated by elevated oxidative stress and is inhibited as soon as the stimulus disappears; but under pathological conditions, the regulation of Nrf2 is altered, making the cell vulnerable to damage. Experimental studies in mice without Nrf2 show an increased incidence of neoplasms and metastasis with exposure to tobacco smoke, pentachlorophenol, and paracetamol as oncogenic stimuli.²⁵

On the other hand, multiple genetic mutations associated with the disruption of the signaling pathway have been found to promote the progression of hepatocellular carcinoma. In a study of samples from 87 patients diagnosed with hepatocellular carcinoma, recurrent mutations were found in 8% of the genes transcribing for KEAP1. Other associated mutations are TP53 in 18%, CTNNB1 in 10%, C16orf62 in 8%, and MLL4 in 7 and 5% in the RAC2 gene.^{25,26} Regarding Nrf2, a study identified the NFE2I2 mutation in 6.4% of a group of 125 patients with hepatocellular carcinoma.²⁷

A cohort study of 107 patients with hepatocarcinoma followed for six years found that reduced KEAP1 expression in hepatocyte cytoplasm and nuclear overexpression of Nrf2 (Nrf2+/KEAP1-) is associated with increased

recurrence and worse prognosis with only 40% disease-free survival at 80 months of treatment with liver resection.^{28,29}

CONCLUSIONS

Oxidative stress plays a fundamental role in the pathophysiology of fibrosis, cirrhosis, and carcinogenesis in the liver. Nrf2 has a dual role; on the one hand, it functions as a major cytoprotectant regulating the synthesis of antioxidant enzymes; on the other hand, overexpression protects not only healthy cells but also tumor cells from oxygen-free radical attack, favoring tumor growth, recurrence, as well as chemo- and radio-resistance, being this duality the object of study, for the pathophysiology of other liver diseases and as a fundamental piece for the diagnosis, prognosis, and treatment at the molecular level of NASH and its progression.

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Common errors in medical journals and how to avoid them

Errores comunes en las revistas de difusión médica y cómo evitarlos

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Keywords:

medical writing,
grammatical errors,
Vancouver standards,
author standards,
references, keywords.

Palabras clave:

escrito médico,
errores gramaticales,
normas Vancouver,
normas para autores,
referencias, palabras
clave.

ABSTRACT

Introduction: scientific research and the publication of a scientific article are two closely related activities. A review was done on how to write a medical article related to writing errors and methodological evaluation errors used to analyze the results. Twenty-seven studies were consulted, using search words: writing, research, errors, cases, method, results, discussion, report, and study habits. The first thing observed when a paper is received for the publication is that most researchers omit the first page, which contains vital information for the control and follow-up of their work. The keywords need to be corrected, with grammatical, spelling, and writing errors, as well as a lack of adherence in the wording of the references, and the absence of a letter of assignment of rights, if applicable. In general, an original scientific article consists of the so-called IMRyD structured format, the initials of the entire article sections. The results and discussion are written in the wrong verb tenses. **Conclusions:** it is essential to comply with the Vancouver norms and the rules for authors of the journal to which the paper is sent.

RESUMEN

Introducción: la investigación científica y la publicación del artículo científico son dos actividades íntimamente relacionadas. Se realizó una revisión acerca de cómo escribir un artículo médico relacionado con los errores de redacción y de evaluación metodológica utilizada en el análisis de los resultados. Fueron consultados 27 estudios, se utilizaron palabras de búsqueda como: redacción, investigación, errores, casos, método, resultados, discusión, informe y hábitos de estudio. Lo primero que se observa cuando se recibe un trabajo para posible publicación es que la mayoría de los investigadores omiten la primera página que contiene información vital para el control y seguimiento de su trabajo. Las palabras clave están mal en general con errores gramaticales, ortográficos y de redacción, además de una falta de apego en la redacción de las referencias, así como la ausencia de una carta de cesión de derechos, si fuera el caso. Por lo general, un artículo científico original consta del denominado formato estructurado IMRyD, que son las iniciales de los apartados fundamentales del artículo. Los resultados y la discusión se escriben en tiempos verbales equivocados. **Conclusiones:** es importante el cumplimiento de las normas de Vancouver, así como de las normas para autores de la revista a donde se envíe el trabajo.

INTRODUCTION

Ruy Pérez Tamayo¹ has pointed out that the genuinely ethical physician: “must perform, to the best of his ability, the following three functions: 1) to care for health and combat disease, always promoting an optimal doctor-patient relationship; 2) to teach his knowledge to students, colleagues, patients, family members and all those who

can benefit from it, and 3) to contribute to increasing knowledge through medical research”.

Scientific research and the publication of scientific articles are two closely related activities. Scientific research ends with the publication of the scientific article; only then will it become part of scientific knowledge.

The publication of discoveries, research, and scientific advances is inherent to science.

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All experiments must be written down so other researchers can contrast, reproduce, and use them. If they were left only to oral transmission, the results would be inaccurate and ephemeral; they would be deformed and lost. A study that is not published is not visible to the scientific community and therefore does not exist.^{2,3}

The three fundamental characteristics of medical language

What are the fundamental mistakes in medical language?

Like all scientific language, medical language does not pursue aesthetic, creative, playful, or recreational purposes -as could be the case with literary language-but informative, didactic, and communicative ones. For this reason, the three main features of scientific language in general, and of medical writing, are truthfulness, precision, and clarity; in other words, what is expressed in a scientific text should not be false, ambiguous, incomprehensible, shocking or cumbersome to read. The severe errors in medical language will go against any of these three essential features - truthfulness, precision, and clarity - that should characterize all scientific language.⁴

When a research paper is received in any biomedical journal, the editor decides whether it continues its evaluation course or is immediately rejected. The main reason for this first instance rejection is because the paper does not conform to the instructions for authors of that journal, starting with its presentation (the form). The objective of this review was to point out the errors in the medical writings, to point out the correct way to correct them and to ensure the work was accepted due to the poor quality of the writing and the methodology used in the results.

Review

A bibliographic review was carried out on how to write a medical article related to writing errors, and methodological evaluation was used to analyze the results. Twenty-seven studies were consulted that dealt with the subject in

Spanish, as well as works related to how to write each of the sections of medical writing. Search words used were writing, research, errors, cases, method, results, discussion, report and study habits.

When a paper is received for possible publication, the first thing the editor notices is that some researchers omit the first page, which has vital information for the control and follow-up of their work, and should contain the following information: 1) short title (cornices) and name the first author followed by et al for the heading of the pages; 2) long title of the research, it should not be longer than 12 (exceptionally up to 15 words); 3) name of the author(s) in a traditional way [(name(s), last name(s)] with numerical superscript from lowest to highest, superscripts of each author if they are from different venues and their maximum academic degree maximum, without positions or headships in case the chosen journal requests it; 4) site(s) where the research originated; 5) address for correspondence of the researcher in charge of this responsibility (does not have to be the first author) and include postal address, telephone and e-mail; 6) attach a letter of assignment of rights in case the journal requires it.

When this first page needs to be included, the article is one step away from rejection

Table 1: Type of articles related to writing a medical article.

Keywords	n (%)
Editorial Staff	11 (39)
Writing and publishing	7 (25)
Error	3 (11)
Results	2 (7)
Title	1 (3)
Method	1 (3)
Discussion	1 (3)
Study habits	1 (3)
Report	1 (3)
Cases	1 (3)
Total	29 (100)

because there is no way to contact the author responsible for the correspondence.

The keywords (up to six) are presented (Table 1). Since almost all authors do not differentiate between charts, tables, and figures, their meaning is presented (Table 2). In the statistical results section, the presentation of the p-value is diverse, and the correct way to do it is shown (Table 3). It should be remembered that in English-language journals, this changes, and even in Mexican journals written in English, the writing varies greatly.

Table 2: Differences between charts, table and figure.

Chart	Expression of numerical relationships, for which there are references or explanations in the text; the data should be arranged so that they can be read vertically
Table	Numerical expressions for which there are no references or explanations in the text, e.g., table of logarithms, and chemical tables, for example
Figure	Expression of images, photographs, maps, and statistical graphs

Source: Sánchez VA, Faulín FFJ, Martínez GMA. *Estadística amigable*. 2nd ed. Editorial Díaz de Santos, S.A. 2006.

Table 3: Errors in describing the p-value.

Error	Correct mode
$p < 0.00000001$	$p < 0.001$
$p = 0.000$	$p < 0.001$
$p = 0.0000$	$p < 0.0001$
$p = 0.0109567$	$p = 0.011$ or $p = 0.01$
n.s (or worse, $p = n.s$)	$p = 0.13$
$p > 0.05$	$p = 0.39$
$p < 0.05$	$p = 0.03$

Adapted from: Barton B, Peat J. *Medical statistics. A guide to SPSS, data analysis, and critical appraisal*; and APA: *Publication Manual of the American Psychological Association*.

Significant errors are varied from grammatical, spelling, and writing mistakes to non-compliance with the Vancouver norms, now *Recommendations of the International Committee of Editors of Biomedical Journals*, which governs almost all national and international medical journals. It is common to find in the references methods different from the Vancouver system, which compromises the medical writing because it generates excess work for correction in case the editorial department does it.⁵

Since the papers received suffer from major flaws, this section discusses the main sections with recommendations for improvement.

Authors

Who is the author? The International Committee of Medical Journal Editors (ICMJE) recommends that authorship should be based on the following four criteria: 1) substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; 2) drafting of the work or critical revision for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be responsible for all aspects of the work to ensure that questions regarding the accuracy or integrity of any part of the work are adequately investigated and resolved. Failure to comply with these recommendations is a breach of professional ethics.⁶

Structure of a medical article

In general, the structure of an original scientific article consists of the so-called IMRyD format, which are the initials of the fundamental sections of the article: Introduction, Methods, Results, and Discussion, which is not an arbitrary publication format, but a direct reflection of the scientific research process that consists of posing a problem, defining a method, presenting the results, and discussing them. Conclusions are included in the discussion section. Other sections are not part of the IMRyD format but are nonetheless important, such as the title, information about the author,

abstract, keywords, acknowledgments, and list of references.⁷

The title

Jara⁸ states that the title should have the following characteristics: be attractive to describe the article's content in a specific, clear, exact, brief, and concise way; enable the reader to identify the subject easily; allow precise indexing of the material. It should have a maximum of 15 words, and using subtitles, abbreviations, or acronyms is not allowed. Keep it brief and between 50 and 100 characters, but no more (shorter titles are more frequently cited).

Recommendation: do not use a colon in the title because the Internet does not recognize the symbol or accept copying titles when downloading references.

The summary (written in the past tense)

It should be no longer than 250 words and generally contain the following points: some journals accept up to 300 words and others up to 150 words, so the journal author's instructions to which the paper is to be submitted should be reviewed. The structured abstract is recommended (IMRyD), and an unstructured abstract can be accepted only in papers that do not require systematization.

Keywords (three to six)

The most significant difficulty was choosing the correct words that accurately defined the paper's main topic, many of which needed to be contained in the paper's title. Others did not appear in the Health Sciences Descriptor (DeCS). In addition, these keywords should be written in lowercase and separated by commas.

The Abstract

Generally, this section should be written in the *Summary* or *Abstract*, in good English as *Introduction*, and as *Background* in narrative reviews.

Keywords: in English. Many authors write this term like this: *Key words* which need to be corrected.

The introduction (written in the present tense).

Evans-Meza R and collaborators⁹ mention some mistakes that can be made and that it is desirable to avoid, such as:

1. Ambitious, overly formal introductions, including endless speeches.
2. Exemplifying introductions or those with plenty of illustrative examples of the subject.
3. Historical introductions, where the historical account of the problem is abused.
4. Introduction solution, in which the results of the research are already announced.

Other authors¹⁰⁻¹³ recommend that the introduction contain at least three paragraphs. The first should be devoted to a review of the literature on the topic to answer the question, "What do we know about it?" It should be limited only to what is related to the purpose of the study. Ensuring that the title's words are included in this space is necessary. The second paragraph should address the problem statement, particularly what we need to learn. The third paragraph should answer the objective of the problem, i.e., answer the question, "What do we want to find out?" The authors suggest using between 10 and 15 references for this part, depending on the type of article. I believe up to five references would suffice in this section.

Materials and methods (written in the past tense)

The technical specifications, exact quantities, and the origin or method of preparation must be included in the material section.

Sometimes it is even necessary to list the relevant chemical and physical properties of the reagents used. Trade names should be refrained from; generic or chemical names are usually preferred. This choice avoids the intrinsic advertising of trade names. In addition, the generic name is likely to be known worldwide, whereas the patented

name may be known only in the country of origin. However, if there are known differences between the patented products and those differences may be of critical importance (as is the case with some growing media), the trade name, with the manufacturer's name, will be essential. When trade names, usually registered trademarks, are used, they should be capitalized (Teflon[®], for example) to distinguish them from generic names. The generic description should follow the trade name: Kleenex[®], tissues.

In the case of methods, the usual order of presentation is chronological. Obviously, related methods should be described together, and a strict chronological sequence may not always be followed, e.g., if a particular test was not performed until late in the investigation, the corresponding method should be described at the same time as the other test methods and not in isolation in a later part of Material and Methods.¹³⁻¹⁶

Avoid

Common errors can make the manuscript uncomfortable to read or cause readers to question the validity of the research. The University of Southern California offers some recommendations:

1. Background information that is not useful should be avoided.
2. Authors should provide a manageable amount of detail.
3. Authors should focus more on how their method met their objective and less on the mechanics.
4. Describe all obstacles and how they were overcome (often included in the "study limitations"). This description will help validate the results.¹⁷

Writing the method can be tedious, but a well-written section can improve the chances of publication and strengthen conclusions. Good luck with the research!¹⁸

Results (written in the past tense)

The aim is to describe in a general way all the information gathered in the research,

organized in a logical sequence, with meridian clarity, without repetition of formats, employing charts (tables) that allow highlighting specific important values and figures (graphs) that help to visualize trends and associations—for the best achievement of these indications, using the mnemonic DECIR (describe, emphasize, complete, interpret, summarize). Use the verb in the past tense for the methods section, except when figures are mentioned.¹⁹ A summary of the content of the results is presented in *Tables 1 to 3*.

Concerning illustrations, these will appear designated as figures for all graphic material: diagrams, drawings, schemes, graphs, photographs (of patients, anatomical pieces, radiographs, electrocardiograms, echocardiograms, ultrasonographic scans, for example). A frequent error is their designation,²⁰ in the text; they are mentioned as fig. or figs.

An excellent way to present the results is through tables, and the elaboration of these tables has its rules; the appropriate way to design a table is presented below, and the content depends on the results. It is recommended that the table's title be in the Arial font at 10 points, the content of the table at 9 points, and if there are many rows or columns at 8 points. The footnote font can be smaller than the text font (and have a different spacing). For example, using double spacing and 12-point Arial font in the text, a font size of 10 points and single spacing can be used.

A common error is that the results are presented as *tables* when they are charts (all English articles use the word *table* indistinctly), not using the word *figure(s)* in photographs, and maps, among others. (*Table 1*).

The discussion (written in the present tense)

What is the discussion section? "The discussion is more difficult to define than the other sections of a scientific article. For this reason, it is also usually the most difficult section to write. Many articles are rejected by journal editors because of poor discussion,

even if the data in the paper are valid and interesting”.

The discussion section is one of the most challenging sections of the scientific article. The following are some suggestions:

1. Begin the discussion with the answer to the initial question, followed immediately by the evidence set out in the results that corroborates it.
2. Write this section in the present tense (“these data indicate that...”) because the paper’s findings are already considered scientific evidence.
3. Include recommendations as appropriate; avoid drawing more interpretations than the results allow.
4. Interpret the data in the discussion and decide whether each hypothesis is supported or rejected; if a decision cannot be made, the researcher must postulate some possible explanations.
5. If the hypothesis still needs to be adequately tested, suggest how the experiment should be modified to achieve this.
6. Explain all observations as much as possible. When referring to the data, it is essential to distinguish the data the own study generated from the observations and publications of other authors.
7. Refer to the work of specific individuals (including yourself) in the past tense; generally accepted facts and principles should be written in the present tense.
8. Decide whether the experimental design adequately addresses the hypothesis and whether it is controlled.
9. Many studies lead to some new questions and open new avenues of research. Suggesting a new hypothesis and the possibility of new experiments is essential to address the central question further. There must be a desire to critically evaluate the decisions made in designing the study and recommend options to others interested in the same problem.
10. Present the reasoning and arguments clearly and validly. No matter how important the research is, the full results will be strengthened if carefully considered and discussed within the article.

11. Analyze and draw a conclusion based on the results obtained.
12. Conclude the discussion with a summary of the conclusions on the contribution of the work.

Considering the complexity of this section and that the author has total freedom to present, confront, highlight, or minimize the impact of his results, it is a section in which it is possible that the author, consciously or unconsciously, influences the facts with his affections and deviates his results by making a discussion that is not entirely neutral (Francis Bacon). This freedom is one of the worst biases that can occur in scientific research, and this section lends itself to it if the researcher does not consider it.²¹

About frequent errors found in medical writings and their correction.²²⁻²⁹

Errors in the wording

Many linguistic errors in medical publications in Spanish is a current problem that deserves attention. Despite numerous scientific writing manuals, finding a scientific article with less than two errors of this type is complicated, which can turn a methodologically impeccable article into a confusing, unintelligible, and unpublishable piece of writing.

A punctuation mark (;) that indicates a pause longer than that marked by a comma and shorter than that marked by a period. It is written attached to the word or sign that precedes it and separated by a space from the word or sign that follows it.

A punctuation mark (:), no space should be left between the colon and the adjacent digits, e.g., 15:30 hours (for this, the period is also used, e.g., 4.1, 2.2). They also indicate a division in mathematical expressions; in this case, they are written with a space separating them from the neighboring digits: 8: 2 = 4. This type of enumeration is characterized by the fact that it always contains an enunciative element, which can be either a word or a syntactic group comprising the content of the enumeration members. For example:

1. I made you dinner: soup and an omelet.
2. The president will discuss essential things for the country: the minimum wage increase and national security.
3. Fresh, clean, and pure: that is what spring water is.

Abbreviations

Whenever abbreviations are essential, they should be written with a period and generally with initial capital letters, for example, acetylsalicylic acid (ASA). The standards agree that when mentioning for the first time, the full name should be written and in parentheses its abbreviations, which can then appear indistinctly in the paper.²⁶ Regarding punctuation, it is recommended that it should not be used so as not to overload the text (ASA).

For a list of standard abbreviations, it is suggested to consult the *Council of Biology Editors Style Guide* or other standard sources.

The period or comma in numbers

The period is used in countries located in the north of the American continent (such as the United States, Mexico, and Canada), in the Caribbean islands, and some countries located in Central America (such as Guatemala and Honduras). However, in French-speaking Canada and Costa Rica, the comma is used. Similarly, the comma is used in countries in the south (such as Venezuela, Chile, Argentina, Colombia, and Uruguay, among others). So, we align ourselves with our geographical location, although the Real Academia Española indicates that in Spanish, the comma should be used, and in English, the period.

The script

When can a hyphen be used between compound words?

1. Surname:
Some surnames are formed with two names simultaneously: Silva-Santisteban, Sánchez-Madariaga, Cerrón-Palomino, Sala-i-Martin,

or Sánchez-Cano. Some journal rules recommend the hyphen between common surnames in contravention of current grammatical rules.

2. First names:
The first name of some people is composed of two names. This practice avoids the first name's second lexeme being considered a surname: Luis-Jorge, José-Alberto, or Tomás-Eloy.
3. Relational adjectives:
In these cases, a hyphen may be used or for a modification of the ending of the first term with "-o." Examples of hyphenated compound words in adjectives: sadistic-masochistic, oral-dental, or infantile-juvenile.
4. Nouns:
This orthographic sign (-) should be distinct from the dash (—). A horizontal stroke represents both, but the hyphen is significantly shorter than the dash. The hyphen is used in the following cases:

a. Join proper names or surnames, common names, and adjectives:

Antonio-Marcos, Sánchez-Cano, Agassi-Sampras confrontation, sofa-bed, city-bedroom*, man-frog*, kilometers-hour, quality-price, cost-benefit, director-presenter, Hispanic-Roman*, French-Canadian*, German-Soviet*, linguistic-literary, theoretical-practical, technical-administrative.*

* They can be written without the hyphen.

b. The hyphen in other graphic combinations:

pages 23-45, academic year 71-72. Dashes can be used to separate pairs or trios of digits that make up telephone numbers: 593-12-83, but in these cases, it is preferable to separate them with blank spaces: 593 12 83 so as not to overload the text.

Examples of hyphenated compound words are airplane-hospital, doctor-surgical, and José-Andrés. Between the years 2014 and 2018, or between the years 2014-2018. Both forms are correct. The conjunction "and" can coordinate two or more members of a period

or interval: "I studied for the master's degree between 2014 and 2018". Likewise, the hyphen can be "the connecting nexus of any type of numerical interval" (*Ortografía de la lengua española*, 2010, ch. III, 4.1.1.1.3.1c): "I studied the master's degree between the years 2014-2018".

In what situation can two names separated by a hyphen be written?

To join first names to avoid the middle name being interpreted as a surname, for example, *Luis-Jorge Camino*, where *Jorge* is the middle name, as opposed to *Luis Jorge Camino*, where *Jorge* is the first surname.

To join compound surnames formed from two simple ones, for example, *María Garrido-Lecca Castro*, where *Garrido-Lecca* is the first surname, versus *María Garrido Lecca*, where *Lecca* is the second surname.

Time period, *time/time-lapse*? Both expressions are redundant, but they can be written. *Time lapse* is even collected by the Academy, although only *lapso* is recommended.

Terms formed with the element *sero-*, which alludes to *sera*, such as *seroprevalence* or *serotype*, are written with that initial and without space or hyphen.

The noun *triage*, used in medicine to refer to the classification of patients according to a system of priorities so they can be provided with the necessary medical care, is spelled with a *J*, not *Triage*.

The compositional element *neuro-*, which comes from Greek and means 'nerve' or 'nervous system', is often used to form terms such as *neurodegenerative*, *neuroscience*, etcetera, preferably written without a hyphen with an initial lowercase letter.

The correct spelling of the name of the bacteria that has affected a thousand people in Germany is *Escherichia coli* or *E. coli*, in italics.

It is correct to write all cardinal numbers less than one hundred in one word, such as *forty-eight*, *thirty-one*, or *seventy-seven*.

The form *pos-* is recommended, both before the vowel (*posoperatorio*) and before

the consonant (*posguerra*), as indicated in the new *Ortografía de la lengua española*.

The word *ratio*, meaning 'ratio or quotient between two numbers', is originally feminine (*la ratio*), although it is accepted as masculine (*el ratio*).

The expressions *dar de alta* and *dar el alta* share the same meaning in the medical context but are constructed with different pronouns: *lo(s)* and *la(s)* in the first case (*lo/la/los/los/las dieron de alta*) and *le(s)* in the second (*le/lles dieron el alta*).

The term *thyroid* can be used in both masculine and feminine (*el/la tiroides*) and always ends in *ese*, so it is advisable not to write *tiroide*.

The acronym *COPD*, which stands for chronic obstructive pulmonary disease, can also be written entirely in lower case, *EPOC*, as a common noun, and not *EPOC*, as a proper noun.

When a figure is followed by a symbol, such as a percentage (%), it is advisable to leave a space between them.

According to Roberto Zavala Ruiz (2005, p. 49) in his book *Sugerencias de redacción*, the articles *el* and *un* should not be placed before expressions of percentage amounts "because they add nothing, are incorrect and blur the typography".

Then it would be incorrect to say, a "**A** 20% of respondents are sick, and **the** 80% remaining are not sick", recommending instead, "20% of respondents are sick, and the remaining 80% are not sick".

Insulin resistance (correct); *insulinresistance* (incorrect).

Tele radiography (correct); *teleradiography* or *tele-radiography* (incorrect).

Manuscript submission

Before sending the manuscript to the editor, it is recommended that at least two people read it. A first review should be carried out by another expert in the topic covered by the article but who is not a co-author of the article.

A general recommendation is to let the article "cool" for several days, or even weeks, before rereading it for the last time. Many

publications include a checklist of key points that must be included for approval.

To get an idea, we can consider the “usual” 8,000 words, especially in review papers, and includes only the IMRyD (not including the first page, abstracts, tables, figures, or references). In a “normal” letter of work, depending on the number of tables, graphs, and figures, these can be between 23 and 25 pages. We will use this last number to make an approximation in the length analysis.^{27,28}

References should be numbered consecutively in the order they were first mentioned in the text. References should be identified in the text, tables, charts, figures, and legends in Arabic numerals in parentheses.

Correct example:

“The possession of concepts and hypotheses matters perhaps less than theoretical availability, the regular exercise of conceptualization, and the habit of constantly formulating varied hypotheses, accompanied by professional circumspection concerning the validity and mode of demonstration”.² The Vancouver standards also accept in-text references in parentheses (1), but I find that they overload the text and prefer the superscript in square brackets.

Another error observed is that multiple references within the text need to be revised. Example: (1, 2, 4, 5, 6, 7, 8, 9) is incorrect; in these cases, it should be written as follows: (1, 2, 4-9).

Journal titles in references should be abbreviated according to the style used by MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals).

Lack of articles: widespread in American literature but inelegant in our language. “*Gestational diabetes is an entity...*”, it would read much better “*Gestational diabetes is...*”, “*Menopause is a syndrome that groups...*”, it would read better “*Menopause is a syndrome that...*”.

1. The scar zone covered the entire inferior aspect, from the apex to the base and from the inferior septum to the posterior LV.

2. The scar area covered the entire inferior aspect, from the apex to the base and from the inferior septum to the posterior LV.

Fillers: repeating a term over and over again.

For example, count 14 “*However*” in seven pages. The same with “*nevertheless*”, “*certainly*”, “*i.e.*”, “*in the same way*”, and “*that is*”. There is also room for the abuse of commonplaces or unnecessary wildcards. It is essential to avoid the often-redundant use of catchwords, such as the adjective “*important*”, for example: “*It is important to begin by saying*”, “*I reiterate*”, “*to foresee beforehand*”, “*to reaffirm emphatically*”, “*main protagonist*”, etcetera.

Plagiarism: voluntary or involuntary. Many problems would be avoided if when “*borrowing*” a text is put in quotation marks or italics, and immediately at the end, its exact reference is cited, or at the beginning of the paragraph, it is acknowledged that they are the words of the author so-and-so.

Inappropriate and abusive use of capital letters: capital letters should be avoided for several reasons: they are challenging to read, slow down reading, and a message full of unnecessary or unjustified capital letters can become tedious for the reader.

1. The initials of the first name or surname must be accented, even if they are written with capital letters (Ángel, Álvaro).
2. Quali-quantitative, not qualiquantitative.
3. Intraarticular, or intrarticular, not intra-articular. The prefixes are permanently attached to the lexical base (intrauterine); therefore, like intramuscular, the word intraarticular is written without a hyphen. It should be noted that the use of the simplified variant intrarticular is admissible (*Nueva gramática de la lengua española*, 2009: 10.3a).
4. Preexperiment, not pre-experiment. When the prefix *pre* is joined to a common and simple noun, it merges into a single spelling with this noun: *preexperimento*, *precrisis*, and *preelectoral*.

- The correct abbreviation for **versus** is **vs**, not **vs** or **Vs**.

CONCLUSIONS

It is vital to comply with the Vancouver norms, the norms for authors of the journal to which the work is sent, and a good dictionary in Spanish and English so that no grammatical, spelling, or writing errors are made in medical writing. Some authors do not recommend this section since, in science, there are never conclusions since science is constantly evolving and everything is still being concluded.

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Polyhexamethylene biguanide dressings in the treatment of a wound. A case report

Apósitos de polihexametileno biguanida en el tratamiento de una herida. Reporte de caso

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Keywords:

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Palabras clave:

polihexametileno biguanida, apósito, heridas crónicas, pie diabético.

ABSTRACT

The diabetic foot has become one of the most important chronic complications of diabetes. One of the treatments that still need to be systematized is polyhexamethylene biguanide (PHMB) dressings because its recent use in wound treatment is recent. We present the case of a patient with an extensive wound in a pelvic limb stump, which was managed with PHMB dressings, presenting complete closure in 11 weeks without the need for surgery. Currently, there is little scientific evidence about the impact of these dressings in treating wounds caused by diabetic complications; however, their routine use could be satisfactory in the closure of chronic wounds, as demonstrated in this case.

RESUMEN

El pie diabético se ha convertido en una de las complicaciones crónicas más importantes de la diabetes. Uno de los tratamientos que aún no se encuentra sistematizado es el uso de los apósitos de polihexametileno biguanida (PHMB) debido a que su uso en el tratamiento de heridas es reciente. Se presenta el caso de un paciente con una herida extensa en muñón de miembro pélvico, la cual fue manejada con apósitos de PHMB, y presentó cierre completo en 11 semanas sin necesidad de cirugía. Actualmente se cuenta con poca evidencia científica acerca del impacto de estos apósitos en el tratamiento de heridas producidas por complicaciones de la diabetes; sin embargo, su empleo de forma rutinaria podría resultar satisfactorio en el cierre de heridas crónicas como lo demuestra este caso.

INTRODUCTION

One of the chronic complications currently considered a public health problem is the diabetic foot because it affects people's quality of life, causes disability, has a high social cost, entails high economic losses, and requires specialized treatment.¹ The prevalence of diabetic foot worldwide varies from 13% in North America to a global average of 6.4%. This prevalence is higher in men than in women. In high-income countries, the annual incidence of diabetic ulcers is about 2%, the most common cause of non-traumatic amputation. In low- and middle-income countries, amputations

are even more common. In 2007, one-third of the global cost of diabetes was allocated to the diabetic foot. In addition, the cost of managing patients with foot ulcers is 5.4 times higher than those without diabetic foot.²

In Mexico, the 2012 National Health and Nutrition Survey (ENSANUT) revealed that the proportion of ulcers was 7.2%, and the proportion of amputations was 2%. In 2016, a significant increase in the proportion of people with ulcers was 9.1%, and the proportion of amputations was 5.5%.³

Prevention, timely detection, and education of patients and their families or caregivers offer the possibility of reducing

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the development of ulcers and amputations, as well as maintaining the quality of life, functionality, and productivity according to each patient's age. Diabetic foot ulcers could be prevented by adequately detecting risk factors, classifying, and applying preventive measures.⁴ Nowadays, there are many instruments to evaluate wounds; however, those with the highest number of prognostic variables in healing should be used, such as patient history, wound size, tissue type, exudates, pain, and signs of infection, in addition to being easy and quick to use.⁵

Treatment involves surveillance of the different etiologies and in-control interventions to improve prognosis.^{6,7} Among the many therapeutic options, surgical debridement, which is the most controlled and efficient technique, and dressings that provide a barrier against external forces and contaminants and promote absorption of exudate around the ulcer, stand out.⁸ There are a variety of dressings available along with more advanced methods to accelerate wound healing;^{9,10} of these, the most commonly used prototype is polyhexamethylene biguanide (PHMB), also known as polyhexanide, classified within bactericidal dressings. It is an antiseptic and disinfectant agent that acts on multiple factors and reduces the probability of bacteria generating resistance mechanisms; it acts against several pathogens, including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas* and *Candida albicans*; it also functions as a barrier that prevents the entry of new microorganisms into wounds and reduces biofilms in the wound bed.¹¹

In 2017, Mancini tested the efficiency of a PHMB dressing to decrease bacterial load in wounds. At seven days, the group of patients with conventional treatment had 21-40% granulation tissue formation, while patients with PHMB had 41-50% in the same period.¹²

PRESENTATION OF THE CASE

We present the case of a 79-year-old male patient with a history of type 2 diabetes and arterial hypertension of 35 years of evolution, with adequate control. He has a history of infracondylar amputation due to a diabetic foot

in 2012, receiving rehabilitation for two years, and being a candidate for prosthesis use.

In August 2019, as a result of the constant trauma of the prosthesis on the residual limb, he developed an ulcer (*Figure 1*), which evolved unfavorably, increasing ischemia and presenting soft tissue necrosis and tibia exposure (*Figure 2*); the reason for which he is presented to the Emergency Department of the General Hospital of Mexico, attended by the General Surgery Service, performing Doppler ultrasound with a report of absence of distal arterial flow in 90%, meriting supracondylar amputation, which was carried out in November 2019 with the following findings: soft tissues without the presence of infection or edema, femoral artery and vein occluded by atheroma plaque in 95% of its lumen. He received antibiotic therapy with amoxicillin/clavulanate 875/125 mg for seven days every 12 hours. He was discharged on the ninth postoperative day; two weeks later, the patient attended a follow-up consultation, showing a significant increase in volume in the stump, erythema and increased local temperature, macerated edges of the surgical wound, and scarce fibrin creations; A thigh X-ray was performed, finding images suggestive of gas, so it was decided to partially remove the suture,



Figure 1: Superficial ulcer.



Figure 2: Tibial exposure and tissue necrosis.

draining 800 cm³ of serous fluid, not fetid and the presence of three tracts, the largest of them in the anteromedial compartment of the thigh of approximately 15 × 8 × 8 cm (Figure 3). A basal wound culture was taken without development. Outpatient treatment was started by irrigation with a physiological solution at 0.9% physiological solution for two weeks, without achieving adequate closure, which is why it was decided to implement management with PHMB dressings, which are internalized in the trajectories, occupying the entire dead space to the outer edge of the wound with prior aseptic technique (surgical soap and sterile saline solution), in addition to debriding fibrin creations of the edges, as well as devitalized tissue with a scalpel; Dressings were changed every five days, observing during each healing the closure of the tracts with the formation of granulation tissue in proximal to distal direction; at four weeks of treatment, a 60% reduction in the size of the wound was observed (Figure 4), using less dressing with complete granulation at each new revision at eight weeks (Figure 5), until presenting complete wound closure 11 weeks after starting treatment (Figure 6). Currently, the patient has no complications of the residual limb and continues to be followed up for systemic pathologies.

DISCUSSION

The reported case deals with a deep non-infected wound that extends beyond the fascia; there is no literature in which PHMB therapy has been implemented in patients with these characteristics, although its use in superficial wounds has been described. Although there are



Figure 3: Dehiscence of the surgical wound. Multiple tracts encompassing muscle fascia are seen.



Figure 4: Wound granulation after four weeks of treatment with polyhexamethylene biguanide.



Figure 5: Wound closure after eight weeks.

national and international guidelines, there is little evidence about routine care. The average time to heal a superficial diabetic foot wound without surgery is approximately 12 weeks. Wound healing is successful when the wound area is reduced to at least 50% of its initial size during four weeks of treatment.

In his study, Elraiyah T mentions that surgical debridement versus conventional management with simple dressings reported a healing rate of 95% in the surgical group,¹³ compared to 79.2% in the group with dressings. In the case we present, complete closure was achieved in 11 weeks, and four weeks after treatment, the patient presented a decrease in wound size of 60%; it should be noted that in our case, we combined both techniques to improve wound characteristics.

Regarding healing days, the surgical group in the Elraiyah T study had a healing time of 46 ± 39 days, the conventional group 129 ± 86 days; in our case, total wound closure was completed in approximately 75 days.¹³

In the study by Sibbald RG in 2011, they used a population and methodology similar to ours. At four weeks, it was found that in the group with PHMB, the mean decrease in wound surface area was 35% versus 28% of the control group; in the case of our patient, the results support their conclusions because it was

observed that wound closure was 60% at four weeks and 100% epithelialization was present at 11 weeks.¹⁴

No infection was identified in our case post-treatment, compared to the report of Elraiyah T, who found up to 12.5% in the dressing group. However, his results were statistically no significant.

Dressings with PHMB are an excellent alternative for treating diabetic foot wounds, used with empirical antibiotic therapy and conventional cures. In the case we present, we observed a reduction and complete closure of the wound, reduction of the infectious focus and the need for surgical reintervention, remodeling of the stump, or even elevation of the amputation level with the use of PHMB, which translates into an improvement in the patient's quality of life, avoiding the risks and trauma inherent to surgical procedures, as well as a reduction in costs, since the total cost of the therapy used was only 74 Mexican pesos.

Following what has been observed in this case and the literature on the benefits of treatment with PHMB for patients with diabetic foot, it is suggested to continue research on the subject, developing a multidisciplinary research protocol and including a significant population to increase the level of scientific evidence

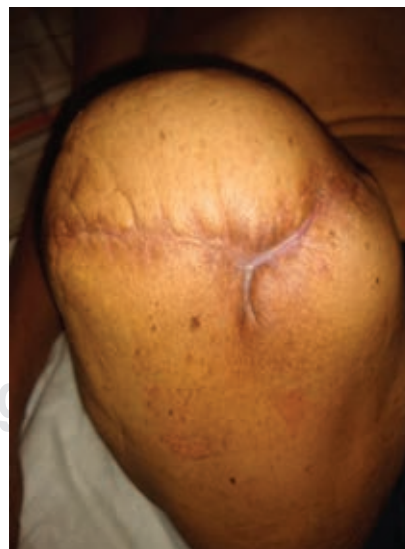


Figure 6: Complete epithelialization of the wound after 11 weeks.

to continue with scientific development and knowledge.

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Cholangiocarcinoma. Case report on the diagnostic approach

Colangiocarcinoma. Caso clínico a propósito del abordaje diagnóstico

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Keywords:

cholangiocarcinoma,
perihilar, Klatskin,
cholestasis, CA 19-9.

Palabras clave:

colangiocarcinoma,
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colestasis, CA 19-9.

ABSTRACT

Cholangiocarcinomas are tumors derived from the biliary epithelium, both intrahepatic and extrahepatic. They constitute the second most frequent primary tumor of the liver. Their presentation in advanced stages characterizes them. There are different important risk factors for developing this pathology; however, up to 50% of cases are reported without an associated risk factor. Diagnosis requires a combination of clinical findings, imaging studies, biopsy or brushing, and tumor markers. The only treatment with curative intent is surgical resection.

RESUMEN

Los colangiocarcinomas son tumores derivados del epitelio biliar tanto intrahepático como extrahepático; constituyen el segundo tumor primario más frecuente de hígado; se caracterizan por su forma de presentación en estadios avanzados. Existen diferentes factores de riesgo importantes para el desarrollo de esta patología; sin embargo, hasta 50% de los casos se reportan sin un factor de riesgo asociado. Para su diagnóstico se requiere del conjunto de clínica, estudios de imagen, biopsia o cepillado, así como de marcadores tumorales. El único tratamiento con intención curativa es la resección quirúrgica.

INTRODUCTION

Cholangiocarcinomas (CCA) are tumors derived from the biliary epithelium, both intrahepatic and extrahepatic.¹ They are the second most frequent primary tumor of the liver.^{2,3} They are characterized by their presentation in the advanced stages of the disease. There are different important risk factors associated with the development of this pathology; however, up to 50% of cases are reported without an identifiable risk factor.³⁻⁷ Diagnosis requires a combination of clinical findings, imaging studies, biopsy or brushing, and tumor markers. The only treatment with curative intent is surgical resection of the tumor. We present the case of a 77-year-old man with typical manifestations suggestive of cholangiocarcinoma.

PRESENTATION OF THE CASE

We present the case of a 77-year-old male patient who reports the removal of nasal polyps 40 years ago as the only relevant history.

His condition began approximately two months earlier with abdominal discomfort, which progressively increased until he presented abdominal pain in the right hypochondrium radiating to the back as a hemi belt and weight loss in recent months. An abdominal ultrasound was performed, and the patient was started on analgesics without achieving total remission of the symptoms. The patient reported choluria, acholia of one month of evolution, and generalized pruritus. One week before, he started with jaundice reflected in his skin and sclerae. He came to the Emergency Department of our institution due to worsening of the symptoms described

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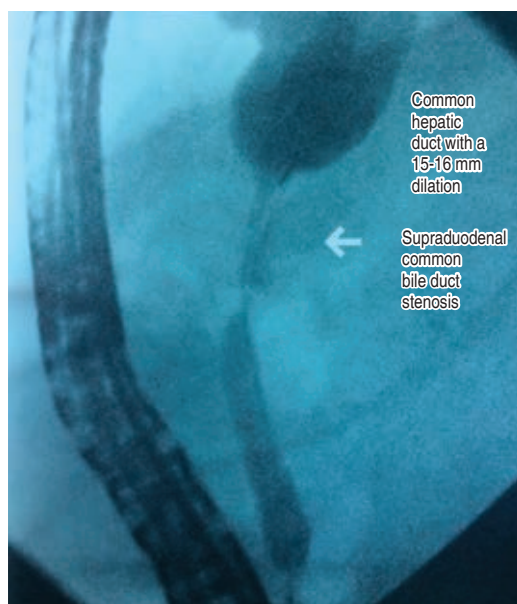


Figure 3: Cholangiography showing a dilated intrahepatic and extrahepatic biliary tract, with a pencil-point narrowing at the supraduodenal level.

A CT scan was performed and reported (Figure 2): "...marked dilatation of the intrahepatic biliary tract, left hepatic of 13 mm, right hepatic of 14 mm, common hepatic duct of 16 mm and cystic duct of 9 mm. There is apparent stenosis of the common hepatic and cystic ducts. No common bile duct is observed; in topography, there is an irregular image of solid appearance, with partially defined contours, with heterogeneous intensification after the administration of contrast medium, which measures 61 × 30 mm and is accompanied by lymphadenopathy at the level of the hepatic hilum. Diagnostic impression: tomographic data suggestive of neoplastic process at the level of the hepatic hilum, which conditions intrahepatic cholestasis, and may correspond to Klatskin's tumor without being able to rule out an inflammatory process".

Due to the CT scan findings, it was decided to perform an endoscopic retrograde cholangiopancreatography (ERCP), which reported the following (Figure 3): "small ampulla of Vater, with ectropion of the ampulla, null biliary

drainage. Intrahepatic biliary tract with severe dilatation. Extrahepatic bile ducts with dilatation of the common hepatic duct between 15-16 mm, pencil point narrowing zone at the level of the supraduodenal portion of approximately 2 cm in length, null biliary drainage. Selective sphincterotomy of the biliary tract was performed, obtaining abundant purulent material and cellular detritus. An endoprosthesis is placed. Conclusion: intrahepatic bile duct dilatation, Klatskin tumor type IV, cholangitis".

Three smears were sent to pathology.

The day after the ERCP was performed, hospital discharge and outpatient management were decided, having remained in the hospital for three days and pending the results of cytology and cytochemistry. Eight days later, he was evaluated in the outpatient clinic with the pathology report: "inconclusive suspicion of malignancy". CA 19-9 marker and liver function tests (LFTs) were requested. Two weeks later, the patient was seen at the outpatient clinic, and the results were reviewed: FA 368 U/l, BT 7.5 mg/dl, BD 5.1 mg/dl, BI 2.4 mg/dl, TGO 62 U/l, TGP 64 U/l, albumin 4 g/dl, and CA 19-9: 1,611 U/ml (normal ranges 0-34).

Since this hospital does not have medical or surgical oncology, the patient moved to another medical facility to receive an oncological evaluation.

DISCUSSION

Cholangiocarcinomas are tumors derived from the epithelium of the bile ducts, which can appear anywhere in the biliary tree.¹ They are classified, anatomically, into intrahepatic (defined as those located proximal to the second-degree bile ducts), perihilar (located in the area between the second-degree bile ducts and the insertion of the cystic duct into the common hepatic, also known as Klatskin's tumors) and distal (those located in the area between the confluence of the cystic to the common hepatic and the ampulla of Vater) (Figure 4).²

They represent 3% of all gastrointestinal tumors and are the second most common primary hepatic tumor after hepatocellular

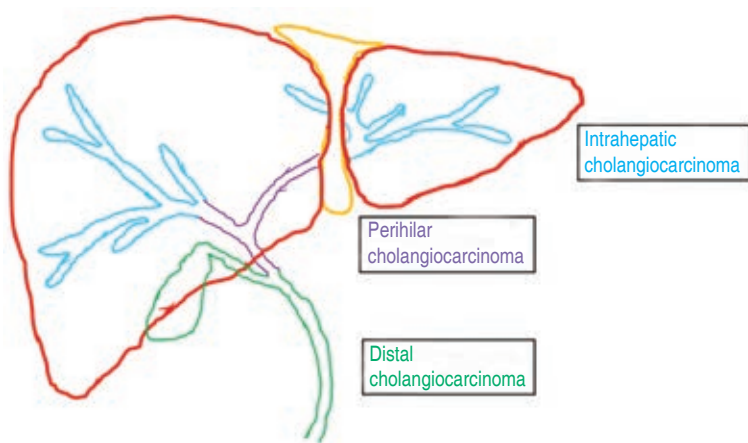


Figure 4: Anatomical classification of bile duct tumor lesions.

carcinoma. Intrahepatic cholangiocarcinomas account for 5-10% of all cholangiocarcinomas, hilar cholangiocarcinomas 60-70% and distal cholangiocarcinomas 20-30%.³

Several risk factors have been established, such as bile duct cysts, Caroli's disease, cholangitis, primary sclerosing cholangitis, hepatolithiasis, cholelithiasis and choledocholithiasis, parasitic infections (by *Opisthorchis viverrini* and *Clonorchis sinensis*), among others.³⁻⁷

However, most cholangiocarcinomas occur sporadically, and about 50% of cases are still diagnosed without any identifiable risk factor.^{3,7}

In this article, we present the case of a 77-year-old male patient who presented to the Emergency Department of our hospital with vague symptoms that, nevertheless, were indicative of cholangiocarcinoma, namely: weight loss, abdominal pain, fatigue, nausea, pruritus, and a cholestatic pattern in the LFTs.⁸ Because early in the disease, the signs and symptoms are unclear and nonspecific, typically patients with cholangiocarcinoma present with cachexia, fatigue, and jaundice, reflecting locally advanced disease or metastasis.⁹ Non-painful jaundice is the most common presenting symptom in 90% of patients with hilar cholangiocarcinoma.¹⁰

Regarding diagnosis, abdominal ultrasound is the initial study of choice since it accurately detects obstruction, extension,

and location within the biliary tree. It is also helpful to rule out the presence of etiologies such as choledocholithiasis or Mirizzi's syndrome.¹¹ The typical findings are dilatation of the intrahepatic biliary tract without dilatation of the gallbladder or common bile duct.⁹ However, it continues to be an operator-dependent technique in which several factors influence an excellent result, such as the operator's experience, the equipment's quality, and the tumor's characteristics.¹²

Regarding tomography, its usefulness lies in categorizing and staging the lesions since its diagnostic certainty in the evaluation of the biliary extension of the tumor is 85%. Additionally, tomography has reasonable certainty in evaluating the severity of portal vein and hepatic artery invasion; however, it is unsatisfactory in evaluating lymph node involvement.¹³⁻¹⁵

Cholangioresonance imaging is considered by many to be the study of choice since it can evaluate the extension of the biliary tract, vascular invasion, local lymphadenopathy, intrahepatic dissemination, and distal metastases. Its positive and negative predictive values for detecting the location and degree of bile duct involvement are comparable to ERCP's.¹³

In this case, it was decided not to perform cholangioresonance imaging since an imaging study already demonstrated and suggested the presence of a tumor, as did the CT scan. It was decided to perform an ERCP instead since the latter being therapeutic and allowing drainage of the biliary tract, benefitted the patient better.

Regarding ERCP, it has a sensitivity and certainty of 91 and 69%, respectively.¹⁴ But in addition, its role in evaluating and managing cholangiocarcinoma is essential since it allows obtaining biliary brushings for cytological evaluation and serves as a therapeutic tool since it can dilate and drain the biliary tract by placing stents.^{14,15}

Of the tumor markers, CA 19-9 and carcinoembryonic antigen (CEA) are the most commonly used markers in diagnosing cholangiocarcinomas. However, CA 19-9 levels show a wide variation in sensitivity

(38-90%) and specificity (50-98%).¹² This marker can also be elevated in patients with cholestasis, liver injury, benign biliary obstruction, and gastric, pancreatic, colorectal, and gynecologic cancers.¹⁶ Obtaining baseline levels of tumor markers helps monitor response to treatment, disease recurrence, and progression.⁹

Brush cytology during ERCP is the most common technique for tissue sampling in patients with suspected malignant biliary strictures. The sensitivity of this technique for diagnosing cholangiocarcinomas is estimated at only 30-60%, in addition to presenting a high proportion of false negatives, which is consistent with what happened in the evaluation of the patient presented in this case. Because of this, a negative brushing should not rule out the diagnosis of perihilar cholangiocarcinoma or delay its treatment.^{11,16} However, fluorescence *in situ* hybridization analysis for chromosomal aberrations associated with perihilar cholangiocarcinoma can significantly increase the sensitivity of brushing up to 90%.⁹

The diagnosis of hilar cholangiocarcinoma requires the presence of a malignant-appearing stenosis in the hepatic hilum and at least one of the following features:¹¹

1. Biopsy or cytology positive for cancer cells.
2. Fluorescence polysomy due to *in situ* hybridization (FISH).
3. Mass-forming lesion in the stenosis seen by tomography or cholangioresonance.
4. CA 19-9 elevation above 100 U/ml

The diagnosis, in most cases, must be inferred by the sum and integration of clinical and imaging studies. Differential diagnoses include choledocholithiasis, benign focal stenosis of the hepatic ducts, Mirizzi syndrome, gallbladder cancer, primary sclerosing cholangitis, autoimmune cholangitis, metastatic disease to the bile ducts or hepatoduodenal lymph nodes (e.g., colorectal cancer).¹¹

Surgical resection is the best available treatment for perihilar cholangiocarcinoma. The type of resection depends on the tumor's location and the anatomy of the bile duct at the

confluence of the hepatic ducts;¹⁷ However, this information is beyond the scope of this article.

An accurate diagnostic approach was performed in time and form in this case. Although a satisfactory sample was not obtained by brushing for cytology, this agrees with the literature reviewed. Despite this, the diagnosis of cholangiocarcinoma could be established when the patient presented a malignant-appearing stenosis in the hepatic hilum and CA 19-9 levels above 100 U/ml.

The "urgency" was resolved by draining the biliary tract by placing a stent through ERCP to reduce the risk of cholangitis associated with the stasis produced by the tumor occlusion.

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Hemocholecyst: laparoscopic approach, case report, and review of the literature

Hemocolecisto: abordaje laparoscópico, reporte de un caso y revisión de la literatura

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Keywords:

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ABSTRACT

Hemorrhagic cholecystitis is a rare complication of acute cholecystitis. We present the case of a 77-year-old male patient with a history of ischemic heart disease, pulmonary thromboembolism, and aortic aneurysm. He was taken oral anticoagulants; he attended the emergency room for presenting abdominal pain; a computed angiogram scan reported active bleeding into the gallbladder lumen and hemoperitoneum, a four-port laparoscopic cholecystectomy was performed, with the following findings: perforated gallbladder, hemoperitoneum, and active intravesicular bleeding. **Conclusion:** hemocholecystitis is a rare pathology, and laparoscopic cholecystectomy is a safe technique for treating this pathology.

RESUMEN

La colecistitis hemorrágica es una complicación rara de la colecistitis aguda. Presentamos el caso de un paciente masculino de 77 años de edad con el antecedente de cardiopatía isquémica, tromboembolia pulmonar y aneurisma aórtico por medio de manejo con anticoagulación oral; acudió a urgencias por presentar dolor abdominal, la angiotomografía computarizada reportó sangrado activo hacia la luz de la vesícula biliar y hemoperitoneo, se realizó una colecistectomía laparoscópica de cuatro puertos, con los siguientes hallazgos: vesícula biliar perforada, hemoperitoneo y sangrado activo intravesicular. **Conclusión:** el hemocolecisto es una patología poco frecuente, la colecistectomía laparoscópica constituye una técnica segura en el tratamiento de esta patología.

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INTRODUCTION

Hemorrhagic cholecystitis is a rare complication of acute cholecystitis. This entity is difficult to detect since its symptoms are easily confused with more common diagnoses.¹ It was first described in 1892 by Naunyn, although it was not until 1938 that Fiessinger and colleagues used the term hemocholecystitis. Since then, there have been only series and case reports of this pathology, with different diagnostic and therapeutic protocols.²

Despite being a rare entity, hemorrhagic cholecystitis with gallbladder perforation and hemoperitoneum has a high mortality.² Ultrasonographic findings may present as acute cholecystitis with indirect signs of complex free fluid, gallbladder fossa hematoma, and intrahepatic hemorrhage.³

PRESENTATION OF THE CASE

A 77-year-old male patient with a history of unspecified ischemic heart disease in 2001. He was managed with the placement

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of two coronary stents and acetylsalicylic acid. Additionally, he had a pulmonary thromboembolism in 2009, treated with acenocoumarin. He also had an aortic aneurysm treated in 2012 with an aortoiliac stent. He went to the emergency department for diffuse abdominal pain of 12 hours of evolution and an intensity 8/10 on the VAS scale, without irradiation nor exacerbating factors, and with nausea without vomiting. The patient self-medicated with butylthioscine and presented partial improvement of 6/10 on VAS scale. Physical examination showed a Glasgow score of 15, oxygen saturation at 90%, arterial hypertension of 211/116, temperature 36 °C, and respiratory rate of 13x'. He had a distended abdomen with signs of peritoneal irritation. Lab tests reported hemoglobin 18.5 g/dL (14.5-18.5), hematocrit 54.4% (42.0-50.0), leukocytes $13.9 \times 10^3/\mu\text{L}$ (4.8-10.0), platelets $170 \times 10^3/\mu\text{L}$ (150-450), PT 42.34 seconds (9.60-12.00), INR 4.33 (0.90-1.20) and TTPa 34 seconds (22-35). Due to the patient's medical and surgical history, the medical team decided to perform a computerized angiography scan. The results showed active bleeding towards the gallbladder lumen (*Figures 1 and 2*), hemoperitoneum, a permeable aortoiliac stent in normal condition, and an obliterated inferior mesenteric artery. The medical team admitted the patient to the intensive care unit for hemodynamic stabilization. The patient

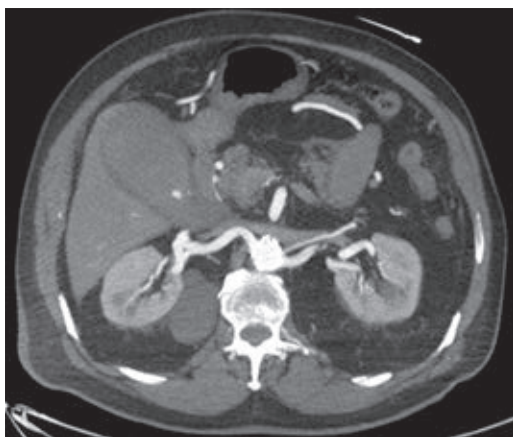


Figure 1: Axial CT scan with arterial phase contrast, showing active bleeding into the gallbladder lumen, which is distended.



Figure 2: Contrast CT scan in the venous phase, showing extravasation of the contrast medium into the gallbladder lumen.

received ix Octapro® (coagulation factors IX, II, VII, and X), two packs of red blood cells, four plasmas, and three platelet apheresis. Two hours after admission, a laparoscopic cholecystectomy was performed.

Surgical technique

Under general anesthesia, the patient was placed in the American position; pneumoperitoneum was performed through a 12 mm trans umbilical port with open technique; a 10 mm subxiphoid port and two 5 mm working ports were placed under direct vision. A diagnostic laparoscopy found a perforated gallbladder, hemoperitoneum, and active intravesicular bleeding (*Figure 3*). Hemoperitoneum and bile were aspirated; zenithal traction of the gallbladder and cystic artery dissection and clipping with Hem-O-Lok® in the cystic artery and duct was done after critical view (*Figure 4*). The gallbladder was resected with a harmonic scalpel, and the surgical piece was removed using an endoscopic bag; the cavity was washed and aspirated. Surgicel® in the surgical bed and a Blake 19 Fr drainage were placed. The working ports were removed, under direct vision, without evidence of bleeding. The aponeurosis and skin were confronted, and the surgical act was concluded. 1,000 mL of bleeding and a surgical time of 100 minutes

were reported. After the surgical procedure, the patient exhibited a favorable postoperative evolution, successfully transitioning to the oral route on the second day. The medical team determined that the patient was ready for discharge on the fifth postoperative day. Pathology reported a gallbladder with acute perforated cholecystitis and transmural necrosis, with no evidence of malignancy.

DISCUSSION

The origin of hemoperitoneum due to gallbladder perforation can be a rupture of the cystic artery or any of its branches, transhepatic perforation of the gallbladder, and bleeding from the margins of the perforation. The presence of hemoperitoneum during gallbladder perforation is very rare.⁴

The patient with gallbladder hemorrhage may present in several ways. Blood may clot

within the gallbladder, resulting in distention of the gallbladder and possibly perforation in the abdomen, leading to peritonitis. Blood may also clot within the common bile duct, resulting in obstructive symptoms. Blood may enter the intestinal lumen, with subsequent hematemesis or melena.⁵

Pathogenesis is an acute necroinflammatory process leading to bleeding. Gremmels et al. described the pathologic findings of acute cholecystitis, which show that intramural inflammation damages the mucosa with infarction and erosion. Rupture of the mucosa may cause bleeding into the gallbladder lumen.⁶

The etiology of cholecystitis involves various factors, including gallstones (accounting for 50% of cases), anticoagulation, anti-aggregation or coagulopathy, gallbladder cancer, trauma, portal hypertension, corticotherapy, blood dyscrasias, ectopic gastric or pancreatic mucosa, and parasites.⁷

Patients receiving anticoagulant therapy have a high risk of hemorrhagic diathesis and may present with symptoms of biliary colic, hematemesis, jaundice, and melena. So, they should be considered with the possibility of hemorrhagic cholecystitis. The clinical picture of hemocholecystitis is nonspecific, and patients may present with pain in the right hypochondrium due to gallbladder distension secondary to cystic duct obstruction by blood clots.⁸

The importance of a thorough initial evaluation in patients with suspected hemorrhagic cholecystitis should be recognized, in addition to performing the indicated radiological studies that help to suspect this rare and challenging manifestation of gallbladder pathology.⁹

Ultrasound findings of hemorrhagic cholecystitis may show thickening of the gallbladder wall, intraluminal membranes, and nonmobile, non-shadowed intraluminal echogenic material. Computed tomography (CT) findings may demonstrate contrast extravasation, high attenuation within the gallbladder lumen, and fluid-fluid stratification.¹⁰

A CT scan with arterial phase can help diagnose and demonstrate the characteristic

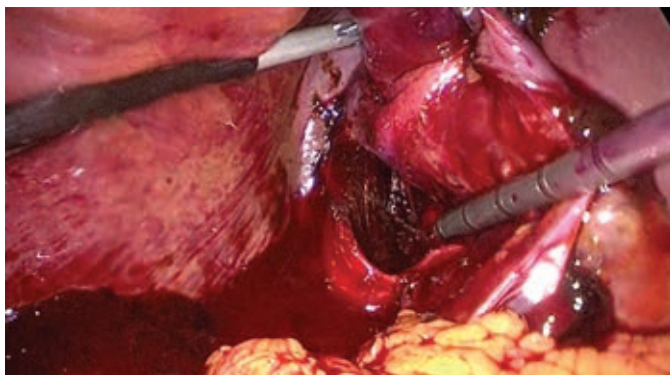


Figure 3: Laparoscopic cholecystectomy with findings of the perforated gallbladder with hemoperitoneum.



Figure 4: Laparoscopic cholecystectomy: cystic artery clipped with Hem-O-Lok®.

findings of wall thickening, distended gallbladder, and heterogeneous materials within it, in addition to active contrast extravasation into the gallbladder lumen.¹¹

Most of the literature reports cholecystectomy as the treatment for hemorrhagic cholecystitis. The literature generally recommends cholecystectomy as the treatment for hemorrhagic cholecystitis. In cases where the likelihood of associated injuries is low, laparoscopic surgical techniques have shown to be a safe option. These techniques can provide definitive treatment without increasing patient morbidity and mortality.¹²

CONCLUSION

Hemorrhagic cholecystitis with gallbladder perforation and hemoperitoneum is a rare entity in gallbladder pathology, establishing a medical challenge for the surgeon dealing with abdominal emergencies. Laparoscopic cholecystectomy is a safe technique in the treatment of this pathology.

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Intestinal malrotation in a 50-year-old adult. A case report

Malrotación intestinal en adulto de 50 años. Reporte de caso

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Keywords:

intestinal malrotation, adult, surgery Mexico.

Palabras clave:

malrotación intestinal, adulto, cirugía México.

ABSTRACT

Introduction: intestinal malrotation is a congenital anomaly associated with a lack of midgut rotation, often related to other developmental anomalies. The condition affects 1% of the population, and medical professionals diagnose it in 90% of cases before one year. However, diagnosing the condition in adults is challenging due to vague and nonspecific symptoms, and in many cases, the only manifestation is high intestinal occlusion. **Clinical case:** a 50-year-old male with a history of early satiety presents symptoms of abdominal distension with peritoneal irritation. An abdominal radiography in a standing position and supine decubitus shows hydro-aerial levels, a stack of coins image, intercat edema, and intestinal dilatation. The medical team performed an exploratory laparotomy to investigate the cause of the symptoms; The surgical team performed the Ladd procedure and observed a spiral arrangement of the ascending colon and ileum, making adequate fixation impossible and increasing the risk of torsion and necrosis. As a result, they decided to perform a right hemicolectomy with an intertransverse anterolateral anastomosis. **Conclusions:** each case should tailor the approach to minimize the risk of complications in the presence of associated congenital anomalies, although Ladd's procedure is the preferred surgical option.

RESUMEN

Introducción: la malrotación intestinal, es una anomalía congénita, asociada a falta de rotación del intestino medio, relacionada con frecuencia a otras anomalías del desarrollo. Afecta a 1% de la población, se diagnostica en 90% de los casos antes de un año de edad; en el adulto el diagnóstico es difícil, pues los síntomas son vagos e inespecíficos, en muchas ocasiones la oclusión intestinal alta es la única manifestación. **Caso clínico:** masculino de 50 años, con antecedente de saciedad temprana, acude presentando distensión abdominal con irritación peritoneal, radiografía de abdomen en posición de pie y decúbito supino con niveles hidroaéreos, imagen en pila de monedas, edema intercat y dilatación intestinal, se procedió a laparotomía exploradora; como hallazgo se encontró malrotación intestinal tipo IIIB; se realizó procedimiento de Ladd, donde se observó colon ascendente e íleon en espiral, con imposibilidad para una fijación adecuada, con alto riesgo de torsión y necrosis posterior; se decidió realizar hemicolectomía derecha con ileotransverso anastomosis laterolateral. **Conclusiones:** el procedimiento de Ladd es el manejo quirúrgico de elección; sin embargo, ante el hallazgo de alteraciones congénitas asociadas, se tendrá que individualizar cada caso, con la finalidad de minimizar los riesgos de complicaciones.

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INTRODUCTION

Intestinal malrotation is an anatomical defect caused by abnormalities in the rotation of the intestine in one of the three stages of embryonic development.

Stage I, rotation is given at 90° within the physiological umbilical hernia.

Stage II, a rotation of 180° occurs during the return to the abdominal cavity, completing the rotation of 270°.

In stage III, the cecum descends from the subhepatic level to the final position in the right iliac fossa; these changes originate between the fifth and twelfth week of gestation.

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Table 1: Midgut rotation abnormalities.

Type	Defect	Clinical effect
IA	No rotation	Midgut volvulus
IIA	Lack of duodenal rotation, regular colon rotation	Duodenal band obstruction
IIB	Reverse rotation of duodenum and colon	Transverse colon obstruction by the duodenal mesentery
IIC	Reverse rotation of the duodenum; normal rotated colon	Right mesenteric pouch (obstruction)
IIIA	Regular rotation of the duodenum; the colon does not rotate.	Midgut volvulus
IIIB	Incomplete fixation of the hepatic angle of the colon	Ladd's band obstruction
IIIC	Incomplete fixation of the cecum and its mesentery	Cecal volvulus invagination (Waugh's syndrome)
IIID	Internal hernias	Paraduodenal hernia

Taken from: Ballesteros GE et al.³

It is considered that midgut rotation anomalies (*Table 1*) present an incidence of one in 6,000 live newborns, and it is more frequent in males than in females; it is essential to know that intestinal malrotation is related to other anomalies, such as intestinal atresia 5-26%, Meckel's diverticulum 1-4%, hernia 7%, and trisomy 21 3-10%.^{1,2}

It affects 1% of the population and is usually detected in 90% of cases before the age of one year.⁴ The clinical manifestations of intestinal malrotation are characterized by biliary vomiting and abdominal distension; as age advances, symptoms become vaguer but may include chronic abdominal pain, weight loss, failure to thrive, and other nonspecific complaints. Adult intestinal malrotation is often asymptomatic and is diagnosed incidentally during a radiological examination for another cause. However, it is common for these patients to report chronic symptoms with a history of episodes of acute pain and cyclic vomiting for years. Many are even labeled as psychological disorders, so diagnosis in adulthood can become complicated. A high percentage of these adults have clinical evidence of malnutrition due to intermittent intestinal occlusions, which alter the venous

and lymphatic drainage of the intestine and produce malabsorption.⁵

High bowel occlusion may be the only clinical manifestation in the adult admitted to the emergency department due to extrinsic compression of Ladd's bands.

PRESENTATION OF THE CASE

The patient is a 50-year-old male, native and resident of Tepotzotlán, State of Mexico, Mexico, with a history of early satiety, when eating food since childhood and without any other added symptomatology.

His condition began 15 days prior to his hospital admission when he presented pain with a visual analog scale score of 4/10, of periumbilical location, gradual, and colicky type, with irradiation to the entire abdomen, of intermittent duration and frequency, aggravated with food intake, attenuated with rest, and accompanied by discrete abdominal distention. The patient's condition worsened two days prior to admission due to constant generalized pain and significant abdominal distention, with the impossibility of passing gas and evacuating; he came to the hospital for management and treatment. On physical

examination, his vital signs were within normal parameters; he was conscious, calm, and oriented in his three neurological spheres, with good skin coloration and mucous membranes, painful facies, and forced attitude. He had an average general constitution, good hydration status, a normal skull without exostoses or sinkholes, cylindrical central neck without adenomegaly, cardiopulmonary without compromise, globose abdomen at the expense of abdominal distension, peristalsis of struggle, tympanic to percussion, with hyperesthesia and hyperalgesia throughout the abdomen, and with generalized involuntary muscle resistance. The rectal examination revealed an empty rectal ampulla.

Laboratory findings are shown in *Tables 2 to 4*. Plain abdominal radiography in the standing position showed the presence of slight bowel distention, inter loop edema with a coin stack image, and hydro-aerial levels without air in the colon (*Figure 1*). Simple abdominal radiography in the supine position

Table 2: Blood chemistry.

Glucose	113.3 mg/dl
BUN	19.9 mg/dl
Urea	43 mg/dl
Creatinine	1.2 mg/dl
Cholesterol	126 mg/dl
Amylase	100 U/l
Lipase	7.7 U/l

BUN = blood urea nitrogen, laboratory tests.
Laboratory tests.

Table 3: Cell blood count.

Hemoglobin	14.6 g/dl
Hematocrit	42.5%
Platelets	324×10^3
White blood cells	13.300 μ l
Granulocytes	87.7%
Lymphocytes	1.1×10^3

Laboratory tests.

Table 4: Coagulation times.

Prothrombin time	14.70*
Partial thromboplastin time	26.70*
INR	1.05
Activity	97.40%
Prothrombin time	14.70*

INR = international normalized ratio.
* Data expressed in seconds.
Laboratory tests.

showed a coin stacking and a duodenal bubble image (*Figure 2*).

Treatment

Due to the poor response to conservative medical management for 24 hours, with the placement of a nasogastric tube and given the impossibility of having a complementary study such as a CT scan of the abdomen, it was decided to go to the operating room to perform an exploratory laparotomy. The preoperative diagnosis was high intestinal occlusion. On surgery, there were findings of intestinal occlusion by extrinsic duodenal compression and incomplete intestinal rotation, with the duodenum located to the right of the midline, Ladd peritoneal bands (*Figure 3*), significant duodenal dilatation (*Figure 4*), and an incomplete fixation of the hepatic angle of the colon in abnormal position. The presence of partial stenosis of jejunum at 15, 25, and 35 cm from the duodenum, two varicose veins of 1.5 cm in diameter, which run along the mesenteric border of the jejunum for approximately 150 cm (*Figure 5*), the jejunum with atrophy in its first 100 cm, and the hepatic angle of the colon located to the right of the midline were identified.

However, despite the lysis of adhesions, the cecum remains in a spiral form without the possibility of fixing it adequately, so a right hemicolectomy with manual anterolateral intertransverse anastomosis was performed. First, the ends of the transverse colon and ileum were closed in two planes: the first



Figure 1: Plain radiograph of the abdomen in a standing position.



Figure 2: Simple radiograph of the abdomen in the supine decubitus position.

with polyglactin 2-0 simple suture, and the second plane was closed with separate Lembert stitches with 2-0 silk. Next, the anastomosis was performed in two planes, the first with polyglactin 2-0 single suture stitches on the posterior aspect of the anastomosis and a Connell Mayo stitch on the anterior aspect; and the second plane was closed

with separate invaginating Lembert stitches with 2-0 silk.

During his hospitalization, the patient had a satisfactory clinical evolution; he restarted the oral route on the fifth day, and was managed with a double antibiotic regimen of ceftriaxone and metronidazole for seven days; at the end of the treatment, he was discharged

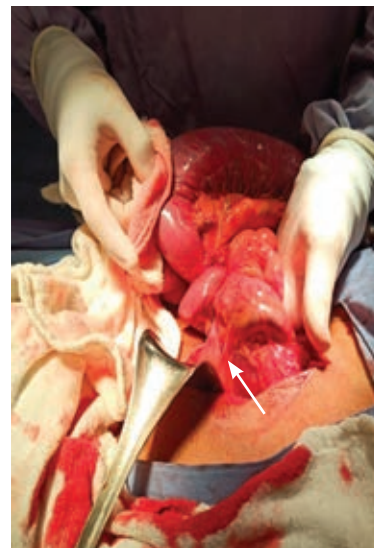


Figure 3: Ladd bands.



Figure 4: The incomplete fixation of the hepatic angle of the abnormally positioned colon is observed.

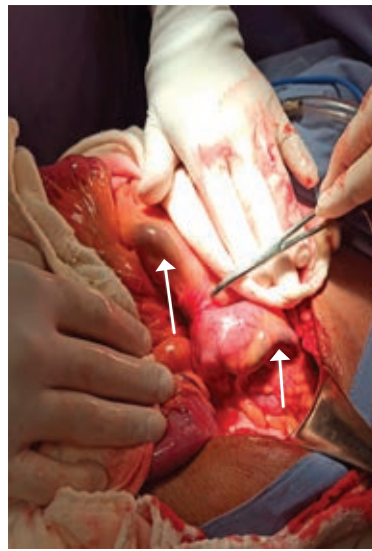


Figure 5: Presence of partial jejunal stenosis at 15, 25, and 35 cm from the duodenum; two varicose veins of 1.5 cm in diameter are seen, running along the mesenteric border of the jejunum for approximately 150 cm.

to continue his outpatient follow-up, with no complications to date.

DISCUSSION

The diagnosis of intestinal malrotation in adults is complex, mainly due to the absence of specific previous signs and symptoms and its low incidence in this age range.⁶ Therefore, most of the time, this pathology is identified during surgery since adults are generally admitted to the emergency department with data of acute intestinal occlusion and, on many occasions, without more specific or specialized studies in some hospital units, which makes immediate surgical intervention necessary to avoid complications.

In newborns, infants, and children up to two years of age, intestinal malrotation should be corrected at the time of diagnosis since it is a surgical emergency; however, in older children and adults, this need is questionable because knowing that one suffers from this developmental anomaly allows immediate action to be taken in the event of any complication and, on the other

hand, the frequency of symptoms at this age is lower.⁷

Consequently, many adults with this pathology, who have been asymptomatic during their lives, present some degree of malnutrition since the presence of chronic volvulus can cause intermittent and sporadic clinical manifestations, alter the venous and lymphatic drainage of the intestine, and produce malabsorption and hypoproteinemia.⁸

The Ladd procedure is the surgical treatment of choice described for the resolution of this anomaly; whereby the volvulus is reduced if present, the intestinal flanges are released, the mesenteric pedicle is widened to prevent midgut torsion, and the small and large bowel are fixed in their usual position, with the performance of a prophylactic appendectomy.^{9,10}

However, in this reported case, and despite performing the maneuvers described above, the patient continued to have the ascending colon and terminal ileum in a spiral form without the possibility of an adequate and safe fixation; to avoid the possibility of intestinal torsion and subsequent necrosis, the decision was made to perform a right hemicolectomy with intertransverse anterolateral anastomosis, which resulted in a satisfactory evolution during his hospital stay and up to the present time.

CONCLUSIONS

Although the literature describes the surgical procedure to be performed in the presence of intestinal malrotation and the existing types of malrotation, the possibility of individual anatomical alterations is always latent. A surgical decision will have to be made according to the case presented, with the sole purpose of minimizing risks and favoring a good evolution for the patient's benefit.

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Perforation of the sigmoid colon secondary to biliary stent migration. Case report

Perforación del colon sigmoides secundaria a migración de endoprótesis biliar. Reporte de un caso

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Rodrigo Urbina-Chapoy,* Rubén Rodrigo Lozano-Salazar*

Keywords:

biliary stent, colonic perforation, sigmoid diverticulum, biliary stent complications, case report.

Palabras clave:

endoprótesis biliar, perforación colónica, divertículo sigmoideo, complicaciones por stent biliar, reporte de caso.

ABSTRACT

The endoprosthesis is a well-accepted therapeutic modality for numerous bile duct diseases. Distal migration is a rare complication that can lead to severe complications. The first perforation of the left colon secondary to a plastic biliary stent was reported in 1996, and since then, forty more cases have been reported. We present the case of a patient who developed an acute abdomen thirteen months after stent placement. The stent was located through a diverticulum in the sigmoid colon during surgery. Primary closure was performed, with a satisfactory clinical outcome, convenient evolution, and discharge due to improvement and an appropriate external follow-up.

RESUMEN

La endoprótesis es una modalidad terapéutica bien aceptada para numerosas enfermedades de la vía biliar. La migración distal es una complicación rara que puede llevar a complicaciones graves. En 1996 se reportó la primera perforación del colon izquierdo secundario a una prótesis biliar plástica, desde entonces se han reportado 40 casos más. Presentamos el caso de una paciente que desarrolló un abdomen agudo 13 meses después de la colocación de una endoprótesis. Durante la cirugía se localizó la prótesis a través de un divertículo en el colon sigmoideos. Se realizó un cierre primario, con un desenlace clínico adecuado, conveniente evolución y egreso por mejoría, así como un seguimiento externo apropiado.

INTRODUCTION

The use of stents for managing bile duct pathology was described in 1980. Since then, their use has become an accepted therapy for benign and malignant biliary tract diseases.¹ One of the complications described concerning the placement of stents, especially plastic ones, is migration, which can be either proximal or distal and occurs in 3 to 8% of patients.^{2,3} Although distal migration in the gastrointestinal tract is followed by spontaneous expulsion of the stent and stool in most cases, it can lead to severe complications such as perforation, abscesses, sepsis, and the development of fistulas.⁴

The first report of a biliary stent that migrated to the left colon and caused a perforation appeared in 1996. The first review about migrated stents with perforation to the left colon was published in 2007, describing one case and reporting 11 more.⁵ By 2014, there were only 25 reported cases in the English literature of biliary stents migrating to the colon.⁶ In most cases, the perforation occurred most often in a diverticulum of the sigmoid colon.

This paper reports a patient with an Amsterdam-type plastic biliary stent that accidentally migrated into the sigmoid colon, causing a free perforation managed with surgery without colostomy.

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CASE PRESENTATION

A 72-year-old woman was admitted to our hospital with a diagnosis of Mirizzi syndrome. Endoscopic retrograde cholangiopancreatography (ERCP) and placement of a 10 Fr 10 cm long Amsterdam-type biliary stent were performed in another hospital. Laparoscopic cholecystectomy was attempted on a scheduled basis, but due to the severe inflammatory process, it was decided to convert to open cholecystectomy. We performed trans cystic cholangiography, identifying a common bile duct filling defect (*Figure 1*). We performed a choledochotomy, the common bile duct stone was removed without the need to mobilize the stent, and a fenestrated subtotal cholecystectomy was performed. A closed suction drain was placed in the subhepatic space. The patient developed a low-output biliary fistula, which was resolved satisfactorily on an outpatient basis without needing specific management. After 15 days, the drainage was removed, management with ursodeoxycholic acid at 15 mg/kg orally was started, and an abdominal ultrasound was requested, which was performed six months later. It showed the intra- and extra-hepatic biliary tract of



Figure 1: Transcystic cholangiography. The filling defect at the level of the common bile duct is appreciated and compatible with Mirizzi syndrome. The stent distal to the obstruction site can be seen.

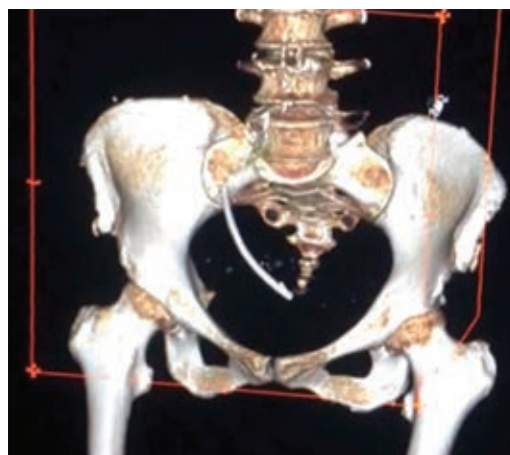


Figure 2: Three-dimensional reconstruction of a CT scan showing a high-density tubular opacity to the left of the midline, consistent with a biliary stent at the level of the sigmoid colon.

standard caliber without other alterations; the prosthesis was not visualized at the level of the biliary tract. Liver function tests (LFTs) showed a decrease in transaminase levels concerning preoperative, with aspartate aminotransferase (AST) 24 U/L versus 35 U/L, alanine aminotransferase (ALT) 28 U/L versus 23 U/L, and alkaline phosphatase (ALP) 111 U/L versus 275 U/L without reaching normal levels, and γ -glutamyl transferase at 108 U/L. No further action was taken.

The patient presented three months later for consultation with clinical data of mild diverticulitis. Laboratory tests were normal, including improved FFP. A physician outside the hospital had initiated management with oral trimethoprim-sulfamethoxazole at an unspecified dose. The antibiotic was continued to complete seven days.

Two months later, the patient presented again with acute abdominal pain. She had signs of peritonitis in the left lower quadrant of the abdomen. Laboratory tests showed leukocytes $16.8 \times 10^3/\mu\text{L}$, serum lactate 2.5 mmol/L, and lactate dehydrogenase 611 U/L. An abdominopelvic CT scan was performed, which showed findings suggestive of diverticulitis complicated with perforation and a hyperdense tubular image measuring approximately 90×5 mm at this level (*Figure 2*).

The patient underwent exploratory laparotomy, where a one-centimeter diameter perforation was found through a sigmoid colon diverticulum secondary to the stent (Figure 3) and multiple uncomplicated sigmoid diverticula. The stent was removed, the intestinal edges were debrided of healthy tissue, and primary closure was performed in two planes, the internal by continuous suture with 3-0 caliber polyglactin 910 and the external through Lembert type stitches with 3-0 caliber silk. There was no evidence of localized or generalized peritonitis, but in any case, a 12 Fr caliber closed suction drain was placed, directed to the parietocolic slide and pelvis. Postoperative evolution was uneventful; ceftriaxone 2 mg every 24 hours intravenously and metronidazole 500 mg every eight hours were administered; the patient was discharged on the fourth postoperative day, with an indication to complete five more days of metronidazole 500 mg every eight hours orally.

DISCUSSION

In our environment, endoscopists most frequently use plastic biliary stents. Patients with these stents require close follow-up for early removal or periodic replacement to avoid obstruction, rupture, infection, or migration. Performing the change every three months is

recommended, although this period can be extended up to six months.

It has been observed that migration occurs more frequently with plastic prostheses than with metallic ones. Distal migration of stents has a variable incidence ranging from 4 to 8%.^{2,3,7} Distal migration is more frequent in cases of benign stenosis of the biliary tract, possibly because migration is favored when the inflammatory process and edema of the biliary tract mucosa disappear.⁴

The most frequent location of distal migration is the duodenum; most distally migrating prostheses pass through the intestinal lumen without complications and are evacuated with feces. On rare occasions, the prostheses do not have a typical passage through the digestive tract and become lodged in the intestinal wall, resulting in a series of complications; the most frequent causes of impaction are considered to be the presence of irregularities of the intestinal wall or the presence of fixation mechanisms of the intestine itself, such as the ligament of Treitz, parastomal hernias, ventral hernias, post-surgical adhesions, and colonic diverticula. Most of the complications associated with stent migration have occurred with straight stents. This type of migration is attributed to the external retention flaps, which cause easier adhesion to the bowel wall, with subsequent pressure necrosis and bowel perforation.⁴

One of the first retrospective studies that looked at the occurrence of prosthesis migration and risk factors was done by Johanson and colleagues, a single-institution retrospective study over four years. In 322 prostheses, they found 16 cases of proximal migration with a rate of 4.9% (95% confidence interval [CI], 3.1 to 8.5%) and 19 distal migrations with a rate of 5.9% (95% CI, 3.9 to 9.2%).²

In another study by Katsinelos and colleagues, the experience of three referral centers in Greece regarding stent migration was revised. In the study period, 378 biliary stents were placed, 57.4% for malignant causes and 42.6% for benign causes. Only 51 (13.5%) stents migrated, and 30 (58.8%) migrated distally, for an overall migration rate of 7.9%. Patients with migration had symptomatology of cholangitis or jaundice, while 13 (43%) patients with distal migration



Figure 3:

The stent is observed at the level of the antimesenteric border of the sigmoid colon.

remained asymptomatic. No colonic perforations were described in this series and only three patients with impaction of the prosthesis at the ileocecal valve.⁷

In another study from a referral center, 524 plastic prostheses were placed in 353 patients over 15 months. The overall migration rate was 8.58%; 21 patients had distal migration, for a distal migration rate of 4.0%. The migration frequency was significantly higher in benign than malignant stenosis (13.7 versus 5.3%, $p = 0.001$).³ As in the previous study, no severe gastrointestinal complications occurred.⁷ The explanation is that a close surveillance policy is carried out in these referral centers, so low morbidity is expected in this way.

In a recent retrospective study by Yuan et al., they sought to determine risk factors for distal migration in plastic prostheses and duodenal lesions. They studied 248 patients with 402 ERCPs and found that the presence of a benign biliary stricture and the length of the prosthesis above the proximal end of the stenosis were determining factors for distal migration; in addition, they detected 25 cases of distal migration, for a rate of 6.2%⁸ (Table 1).

Of the 42 cases reported in the literature, only six have been treated with primary closure,⁹⁻¹³ as in our case, and one was performed laparoscopically.¹⁴ Primary closure can be performed when an early diagnosis is made or when there is a high index of suspicion. None of the patients treated with primary closure had a fatal outcome (Table 2).

Table 1: Incidence in the literature of biliary stent distal migration.

Author	Patients (N)	Distal migration (N)	Incidence (%)
Johanson ²	378	19	5.9
Katsinelos ⁷	378	30	7.9
Arhan ³	524	21	4.0
Yuan ⁸	402	25	6.2

CONCLUSIONS

Distal migration to the colon of a biliary stent is a rare medical event, but most occur without any sequelae; however, they may lead to severe complications.

Sigmoid colon perforation secondary to migration of a biliary prosthesis is a rare complication. It should be suspected in patients with acute abdominal pain and an

Table 2: Cases treated by primary closure.

Author	Age	Gender	Diagnosis	Benign biliary stenosis	Perforation site	Perforation of diverticulum	Death
Lenzo ⁹	82	Female	Cholangitis Choledoco-lithiasis	No	Sigmoid	Yes	No
Storkson ^{14*}	86	Male	Lemmel syndrome	No	Sigmoid	No	No
Senosiáin ¹⁰	80	Female	Cholangitis Choledoco-lithiasis	No	Sigmoid	No	No
De Andrés ¹¹	70	Male	Choledoco-lithiasis	No	Sigmoid	Yes	No
Marcos ¹²	65	Female	Choledoco-lithiasis	No	Sigmoid	Yes	No
Ponce ¹³	65	Male	Choledoco-lithiasis	No	Rectosigmoid junction	No	No
Osorio [‡]	72	Female	Síndrome de Mirizzi	No	Sigmoid	Yes	No

* Case treated by laparoscopic surgery. ‡ Present case.

ERCP history. Early surgery is recommended to avoid potentially dangerous complications that may lead to death. Suppose perforation caused by a stent is confirmed. In that case, a primary closure may be done to avoid a colon resection or the realization of a stoma if the patient's clinical conditions allow it.

Patients with benign bile duct stenosis have a higher frequency of distal migration. In contrast, patients with previous surgeries, wall hernias, stomas, and diverticular colon disease are at risk of developing complications secondary to distal migration of the stents.

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