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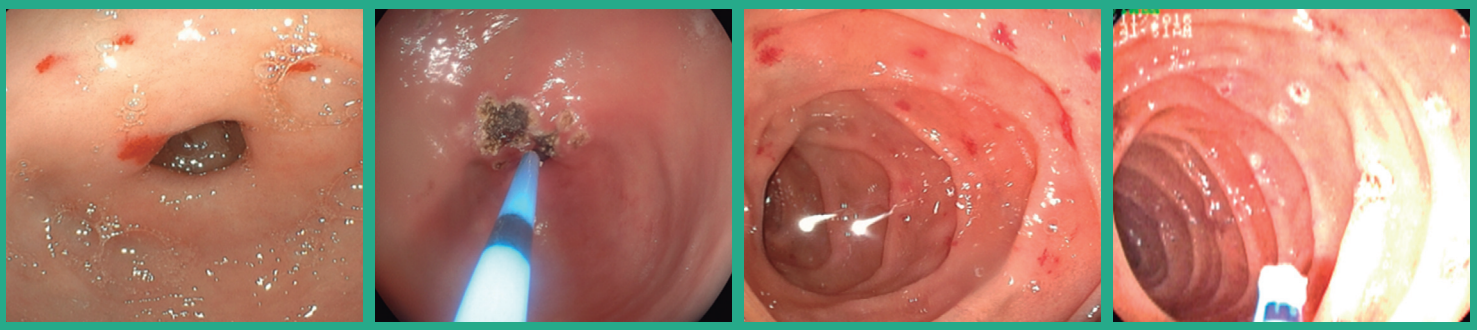

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Case report

Cover: *A. Telangiectasias in the antrum.*
B. Argon plasma therapy on lesions in the antrum.
C. Telangiectasias in the small intestine.
D. Argon plasma therapy.
Courtesy by the authors: Gabriel Alonso Mosquera-Klinger, Kenny Gálvez Cárdenas, Ana María Valencia.
Article: Diagnosis and treatment of patients with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber-syndrome) at a university hospital in Colombia

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Comparison of two periods in liver transplantation at Colombian medical center

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Abstract

Objective: Liver transplantation is the treatment of choice for acute and chronic liver failure. Liver transplantation results have improved in recent years, so the objective of our work was to compare results from two different periods of time at a center in Colombia. **Patients and Methods:** This is a retrospective descriptive study comparing first time adult liver transplant patients from 2004-2010 (Series 1: 241 patients) and from 2011-2016 (Series 2: 142 patients). **Results:** The average patient age was 54 years, 57% were men, and the average MELD score was 20. There were no significant differences between the characteristics of donors and recipients from one period to the next. The main indications for liver transplantation were alcoholic cirrhosis and cryptogenic and autoimmune hepatitis. Series 2 contained fewer hepatitis B and C cases than did Series 1. Thirty percent of the patients had hepatocellular carcinoma. The one-year survival rates were 81% in Series 1 and 91% in Series 2, whereas five-year survival rates were 71% and 80%, respectively. The main causes of death were cancer, cardiovascular disease and sepsis. From the first period to the second period, there was a significant increase in biliary complications but no differences in infectious complications, vascular complications or cellular rejection. **Conclusion:** Short and medium term liver transplantation results at this center in Colombia have been excellent, but there have been significant improvements in patient survival rates in recent years that are similar to those reported elsewhere in the world.

Keywords

Liver transplant, cirrhosis, liver graft, rejection, retransplantation.

INTRODUCTION

Liver transplantation is considered to be the treatment of choice for cirrhotic patients with chronic liver failure with complications, for acute liver failure with poor prognosis, and for hepatocellular carcinoma within the Milan criteria. (1) In recent years improvements in the care of patients after liver transplantation have been associated with higher survival rates for both patients and liver grafts. Some years ago we reported the experience of our center in Colombia and described survival rates and complications similar to those described in the American and European registries. (2, 3, 4) With increased survival of patients after liver transplantation, there is now special concern for medium and long-term survival as well as interest in strategies to reduce complications and improve patients' quality of life. (5) The objective of this study is to evaluate liver transplantation results in recent years and compare them to results obtained in the previous study. (2)

PATIENTS AND METHODS

Three hundred five liver transplantations were performed at the Hospital Pablo Tobón Uribe in Medellín Pablo Tobón Uribe Hospital from February 2004 to December 2010. Of these, 241 were first time procedures in adult patients,

the results of which have already been published. (2) One hundred sixty liver transplantations were performed from January 2011 to December 2016. Of these, 142 patients were first time procedures. Patients who underwent liver retransplantation, combined liver-kidney transplantation and other combination of organ transplantation were excluded. All donors were cadavers.

This is a retrospective and descriptive study for which information was obtained through reviewing medical records and the liver transplant database. It was authorized by the hospital's ethics committee. The severity of liver disease was staged in all patients with the Child-Turcotte-Pugh (Child) score and the Model for End-stage Liver Disease (MELD) score. All patients with hepatocellular carcinoma had to meet the Milan criteria to undergo transplantation. Individuals with acute liver failure were transplanted when they met the poor prognosis criteria of King's College hospital. Conventional immunosuppression consisted of administration of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil and steroids. The latter were suspended three to six months after the procedure. In our protocol the antimetabolite is not suspended in order to reduce the calcineurin inhibitor to the lowest possible dose. When the donor was positive for cytomegalovirus immunoglobulin G (IgG) and the recipient was negative, the recipient was given universal prophylaxis for CMV. In the past, individuals without a high risk profile for CMV did not undergo any intervention, but following current international protocols, we chose preventive follow-up. (6) Patients with risk factors for fungi received prophylaxis with fluconazole, and those with high risk of Aspergillus infection (retransplant or dialysis patients) received prophylaxis with echinocandin. Patients with chronic hepatitis B infections continued with Entecavir or Tenofovir. Immunoglobulin was used intramuscularly in patients at high risk of recurrence of hepatitis B, although in recent years immunoglobulin has not been used against hepatitis B in individuals with negative viral loads, negative "e" antigen and those who are receiving adequate antiviral treatment. (7)

Prior to transplantation, patients with chronic hepatitis C infections with Child A liver cirrhosis were treated with antivirals available at the time (PEG interferon alpha, ribavirin, boceprevir, or telaprevir). However, most patients received treatment following transplantation as well due to the degree of liver dysfunction. In cases of moderate to severe acute rejection confirmed by biopsy, patients were given methylprednisolone boluses and baseline immunosuppression was adjusted. Patients with renal dysfunction who were not candidates for combined liver and kidney transplant as well as patients who were Child B or C with severe ascites received 20 mg of basiliximab on days 0 and 4 to allow late introduction of the calcineurin inhibitor. All patients with poor initial function or no primary function were cataloged as having primary hepatic graft dysfunction. Piggy-back vena cava surgical technique was used without need for venovenous bypass in any patient. Conventional biliary anastomosis was performed by choledochocholedochostomy without using a T-tube but with hepatic-jejunostomy depending on the criteria of the transplant surgeon. In the postoperative period, all patients were transferred to the intensive care unit (ICU) with an early extubation protocol.

Statistical analysis was based on patients' sociodemographic and clinical variables including pre-transplant conditions, liver disease etiology, severity of condition classified by Child and MELD scores, intraoperative and postoperative variables, complications, ICU days, hospital stay, graft survival and patient survival. Initially, the type of distribution of the variables was verified and a bivariate analysis was performed using Pearson's χ^2 test for categorical variables and the non-parametric Mann-Whitney U test to compare the ranges between independent groups. A survival analysis was performed using the Kaplan-Meier curve for graft losses and patient deaths at one and five years.

RESULTS

The average age of the recipients was 54 years, 57% of the recipients were male, the average MELD score was 20, and there were no differences donor and recipient characteristics between the two periods (Table 1). Liver disease etiology is described in Figure 1. The most frequent causes were alcohol cirrhosis, cryptogenic cirrhosis and autoimmune hepatitis cirrhosis. Comparison of the two series showed a reduction of liver transplantation for hepatitis B or C, but it was not significant. Hepatocellular carcinoma was the reason for transplantation in 25% of the cases in Series 1 (2004 -2010) compared to 30% of the patients in Series 2 (2011-2016) but the difference was not significant. Other causes include hemochromatosis, polycystic liver disease, epithelial hemangioendothelioma, Budd-Chiari syndrome, Wilson's disease, congenital liver fibrosis and acute intermittent porphyria.

Choledochocholedochostomies were performed in 92% of patients. It was necessary to place an arterial graft for the hepatic artery in 4% of the patients. The length of ICU stay was 3 days, and the hospital stay was 14 days, without statistically significant differences. At one year, 81% of the patients in Series 1 were still alive while 91% of the patients in Series 2 survived the first year. This difference is statistically significant ($p = 0.04$). The five year survival rates were 71% for Series 1 and 80% for Series 2. This difference is not statistically significant ($p = 0.07$) (Figure 2). The 5-year liver graft survival in Series 2 was 75% without statistically significant. The main causes of death were cancer, cardio-

Table 1. Characteristics of liver transplant donors and recipients at Hospital Pablo Tobón Uribe

Variable	2004-2010 (n = 241)		2011-2016 (n = 142)		*p*
	Mean (± SD)	Median (min-max)	Mean (± SD)	Median (min-max)	
Age (years)	51.8 (±12.5)	55 (15-72)	51.5 (±12.7)	54.5 (16-70)	0.91
Male/female	61.8/38.2		57/43		0.21
Child-Pugh	9.6 (±2.3)	10 (6.0-15)	9.2 (±2.9)	9 (5-29)	0.07
MELD	18.7 (±5.3)	18 (8-33)	19.7 (±6.8)	20 (6-40)	0.71
Donor age (years)	35.1 (±13.2)	34 (2-67)	34.5 (±13.7)	33 (8-60)	0.62
Waiting list time (days)	32.3 (±39.7)	21 (1-280)	31.9 (±49.5)	15 (1-415)	0.16
Cold ischemia (minutes)	352.5 (±108.1)	330 (165-910)	338.4 (±91.5)	335 (159-632)	0.31
Hot ischemia (minutes)	28.0 (±7.8)	27 (15-90)	28.6 (±6.7)	28 (17-51)	0.25
Hospital stay (days)					
Intensive care	4.5 (±6.8)	3.0 (0.0-64.0)	4.1 (±5.1)	3.0 (1.0-44.0)	0.30
Total hospital stay	14.3 (±13.0)	11.5 (0.0-104.0)	15.7 (±11.6)	14.0 (1.0-96.0)	0.06

SD: standard deviation; MELD: Model for End-stage Liver Disease

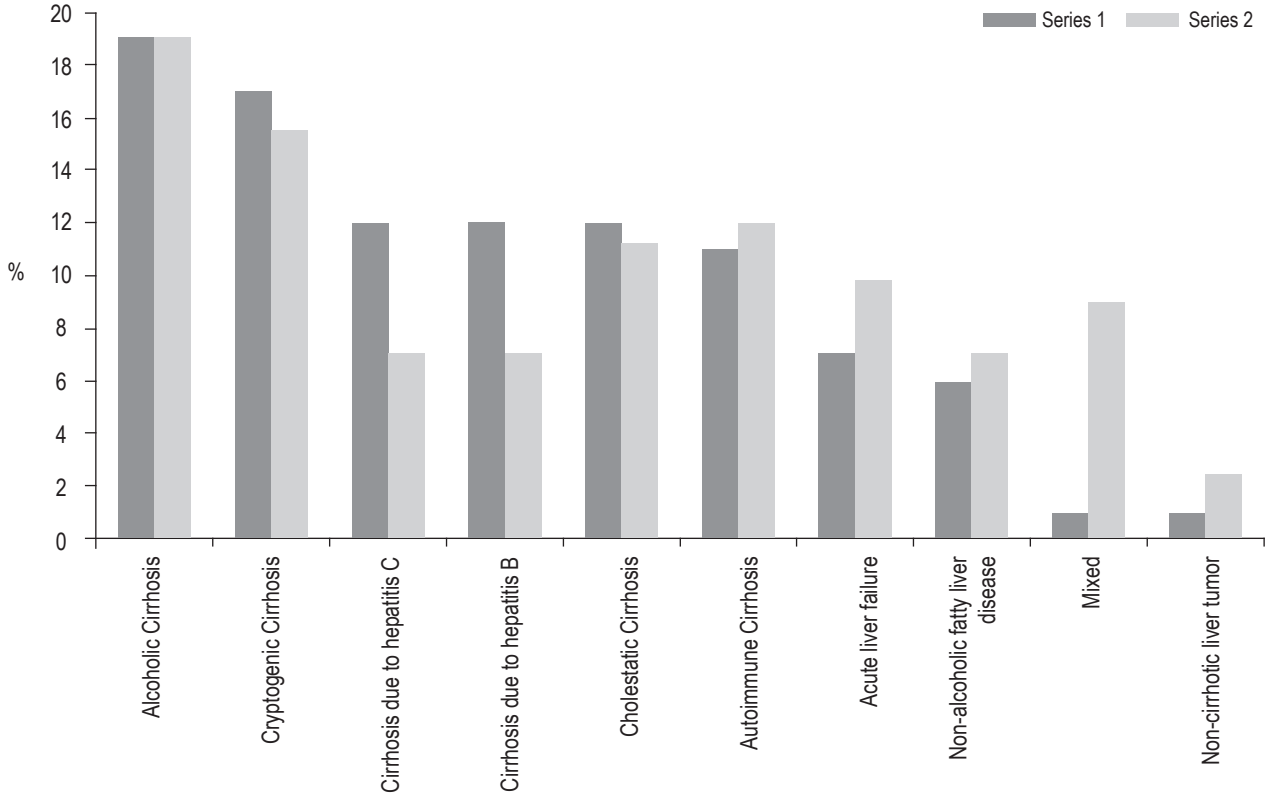

Figure 1. Etiology of liver disease in liver transplant patients

vascular disease and sepsis. Compared to Series 1, there was an increase in death due to neoplasms and cardiovascular causes in Series 2, with a decrease in deaths due to sepsis and bleeding, but there were no statistically significant differences (Figure 3).

A summary of perioperative and post-transplant complications is found in Table 2. Postoperative bleeding occurred in 21% of patients, and primary hepatic graft dysfunctions were found in 4.9% without differences between the series. There were no differences in vascular complications bet-

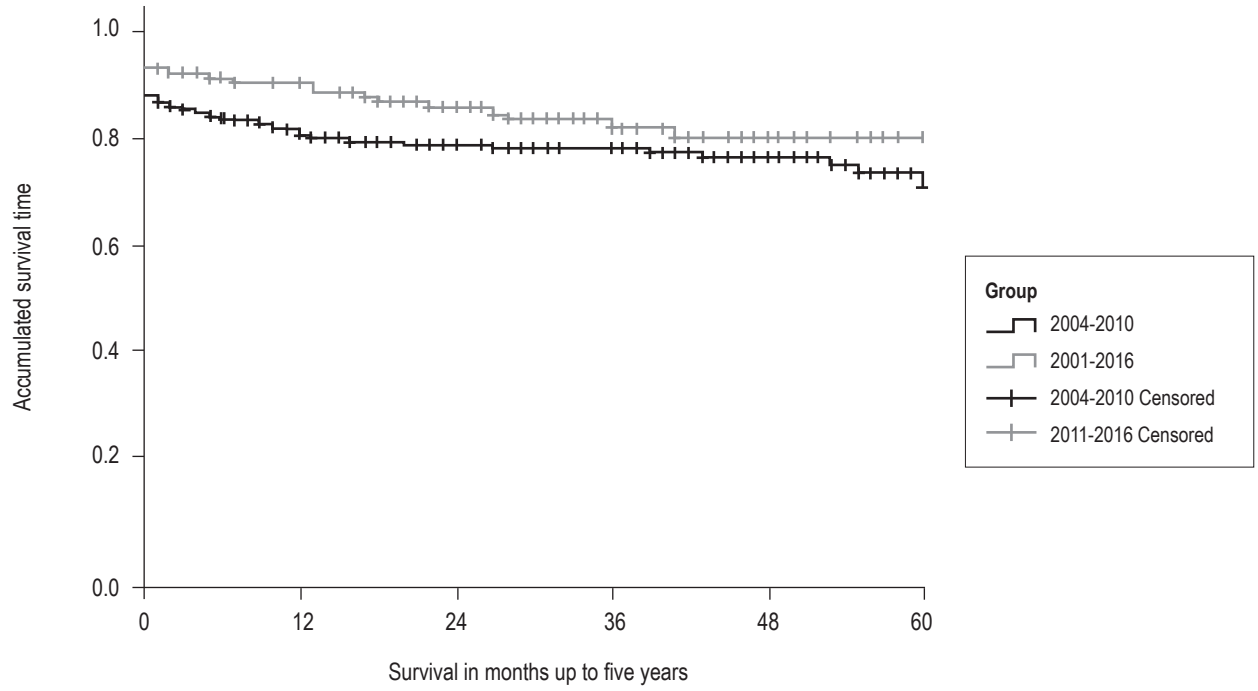

Figure 2. Survival in two liver transplant series from the Hospital Pablo Tobón Uribe.

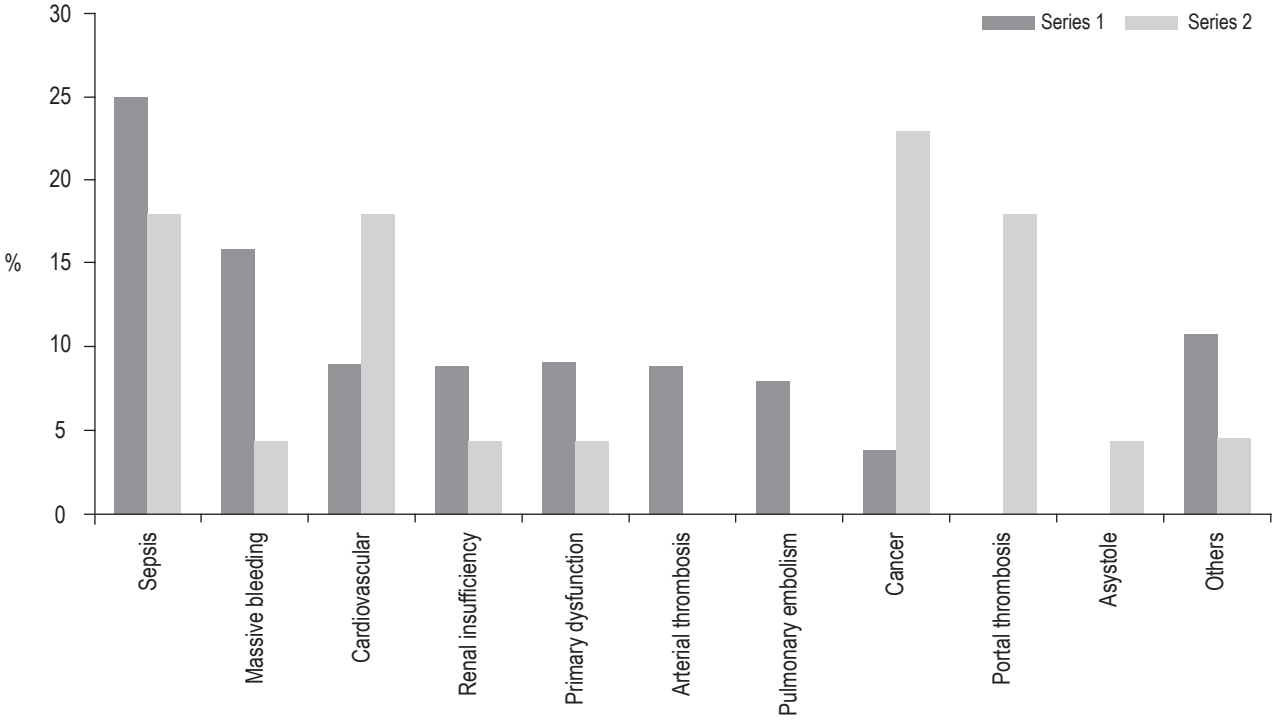

Figure 3. Causes of death following liver transplantation in patients at the Hospital Pablo Tobón Uribe.

Table 2. Post-transplant complications in patients at the Hospital Pablo Tobón Uribe

Complication	2004-2010		2011-2016		*p*
	No.	(%)	No.	(%)	
Perioperative					
Bleeding	63	(26.1 %)	30	(21.1 %)	0.342
Primary dysfunction	11	(4.6 %)	7	(4.9 %)	0.945
Reperfusion syndrome	3	(1.2 %)	4	(2.8 %)	0.489
Vascular					
Arterial	14	(5.8 %)	7	(4.9 %)	0.715
Hepatic vein	14	(5.8 %)	7	(4.9 %)	0.715
Portal vein	14	(5.8 %)	7	(4.9 %)	0.715
Bile	36	(14.9 %)	40	(28.2 %)	0.002*
Infectious					
Bacterial	82	(34.0 %)	46	(32.4 %)	0.918
CMV	24	(10.0 %)	23	(16.2 %)	0.123
Herpes	16	(6.6 %)	8	(5.6 %)	0.926
Fungal	7	(2.9 %)	3	(2.1 %)	0.895
Tuberculosis	2	(0.8 %)	2	(1.4 %)	0.851
Not specified	105	(43.6 %)	0	(0.0 %)	0.000*
Rejection	76	(31.5 %)	35	(24.6 %)	0.151

* Statistically significant difference.
CMV: cytomegalovirus.

ween the series. Biliary complications occurred in 28.2% of the patients in Series 2 but in only 14.9% of the patients in Series 1. The difference was statistically significant (p = 0.002). Eighty percent of these patients had anastomotic stenosis while 65% were early. Bacterial, herpes viral, fungal and mycobacterial infections did not differ significantly from what was reported in the previous series, although there was a slight increase in cases of CMV infections (16% vs. 10%). The foci of bacterial infection were abdominal in more than 50% of cases with urinary, pulmonary, soft tissue and bacteremia infections accounting for the rest. It should be noted that the only cases of disseminated toxoplasmosis and disseminated strongyloidiasis ever documented in our institution after liver transplantation appear in Series 2.

Acute rejection was confirmed by biopsy in 24% of cases, and no cases of chronic rejection were documented. There were no differences with Series 1. Hepatic retransplantation was necessary in 4.9% of patients showing a stable rate since in Series 1 it was 6.6%.

Hepatocellular carcinoma recurred in 5% of cases as in the first series. The cause of death in all cases was recurrence that occurred in the first year with extrahepatic disease and rapid evolution. The other death-related neoplasms were post-transplant lymphoproliferative syndrome in two patients and lung cancer in one patient. The presence of skin cancer was documented in three patients but had no impact on survival.

DISCUSSION

Liver transplantation has evolved in recent decades and is accepted as a first-line therapeutic option for patients various different liver diseases thanks to the results currently being obtained. (1, 8) The most relevant result of this study is the increased 1 and 5 year survival rates. The latter is 80% higher than the rate previously reported by our center. (2) It is comparable to the rate reported in the most recent update of the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR) in the United States as well as those reported by referral centers in the United States and Europe. (9) This is relevant if you consider the multiple problems that exist in a country of limited resources like Colombia. We believe that the good results obtained are the product of advances in knowledge and experience of our liver transplant surgical and medical group in recent years.

This study's short and medium term survival results are the best that have been reported in Colombia and according to our search of databases are also the best reported in Latin America. A recent study from another transplant center in Colombia has also reported good results including a 5-year survival of 79%, but patients who died during the first 30 days (15% of that cohort) were not included in that study which may bias the results. (10) Other reports from the region include those of Meirelles et al. collaborators from Brazil, who presented experience at the Albert Einstein Israelite Hospital where a 5-year survival rate of 74.3% was achieved. (11) Mattos et al. found a 5-year survival rate of 53% in southern Brazil, (12) a multicenter study in Argentina found a 1-year survival rate of 81%, (13) and a study at the Austral Hospital of Buenos Aires found a 5-year survival rate of 76. % (14).

Very recently, an international multicenter study by Muller et al. reported analysis of 7,492 liver transplant patients between 2010 and 2015 which aimed to find the best possible results in an "ideal" low risk liver transplant cohort from experienced centers in an effort to define objective references in clinically significant results after liver transplantation. (15) The low-risk cases were patients with MELD scores of less than 20, first transplantations, cadaveric donors due to brain death, and a low balance of risk (BAR) score. Based on these data, they determined that transplantation in patients with these characteristics should obtain 1-year survival rates over 90%, ICU stays

of less than 4 days, hospital stays of less than 18 days, and retransplantation rates of less than 4% . These data were comparable with our results and confirm the progress of our group. It should be noted that the characteristics of most of our donors are good and the waiting times are short, both of which impact results favorably.

A very important shift in the causes of death that has occurred in recent years should be underlined: cancer and cardiovascular diseases are the most frequent causes of death in this study as well as in data reported elsewhere in the world. (16, 17) Sepsis and bleeding, which were the most frequent in our first series, have both decreased. This is related to better perioperative care and greater surgical experience. Based on these results, we decided to adjust our post-transplant protocol by adding oncological screening according to the characteristics and risk factors of each patient. Series 2 reports deaths from portal thrombosis. These occurred early, so other treatment options and liver retransplantation by extension to the superior mesenteric vein were not options. Portal thrombosis had been an absolute contraindication to transplantation in our center, but in recent years, we began to perform liver transplantation in patients with this condition, and there were problems in the selection of this subgroup of patients.

Infectious complications remained stable over time, although there was a slight increase in CMV infections in Series 2. Analysis of the data shows that these infection rates were not only comparable to those reported in the literature but were actually lower. (18) Based on previous results, we decided to extend the strategy of universal prophylaxis from high-risk individuals towards preventive follow-up protocol in patients with intermediate risk of CMV infection. The rates of mycobacterial and fungal infections have remained low, and it should be noted that no invasive candida infections have been documented in recent years even though prophylaxis was directed exclusively at high-risk individuals.

The main change with respect to post-transplant complications was the significant increase in biliary complications, specifically anastomotic stenosis. An analysis of this situation made with the medical and surgical group found no objective explanation for this increase. To reduce biliary complications, we have since adopted the strategy of temporarily leaving a Nélaton probe in the bile duct for the first weeks after transplantation whenever there is a doubt about anastomosis. This has been related to a decrease in the rate of biliary stenosis (unpublished data).

The survival rate of transplant patients with hepatocellular carcinoma was similar to that of other patients. Recurrence rates were below 10% and in accord with what has been reported in the world literature when the Milan criteria are met. (19)

As in other Latin American countries, alcoholic liver disease was the main indication for liver transplantation in our series. This has remained stable over time. Of liver disease etiologies, we should highlight autoimmune hepatitis which we know occurs frequently in our environment even though we do not have incidence and prevalence studies for Colombia. Recently, Díaz Ramírez et al. described the characteristics of 278 patients of which 10% required liver transplantation. (20) In this study, we document a reduction in the indication of liver transplantation for hepatitis B and hepatitis C which we associate with better available treatment options. This is something that we hope to improve in the next years. These findings coincide with current reports from elsewhere in the world.

Limitations of this study include its single-center design and exclusion of retransplant patients, combined liver-kidney transplant patients, and other multiple organ transplant patients due to the difficulties of comparing characteristics of these patient groups.

In conclusion, liver transplantation is an effective first-line therapy for various acute and chronic liver diseases in selected patients. Short and medium term results at the Hospital Pablo Tobón Uribe in Medellín are comparable to those obtained in the United States and Europe.

Conflict of interests

None of the authors have conflicts of interest.

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Transanal minimally invasive surgery (TAMIS): technique and results of initial experience

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Abstract

Background: Transanal endoscopic surgery, a recently described minimally invasive approach, provides superior exposure and access to the entirety of rectal lesions and has lower risks of compromising resection margins, lower recurrence rates and lower morbidity and mortality than do conventional transanal excision and endoscopic removals. **Objectives:** The aim of this study is to describe our initial experience and with minimally invasive transanal surgery (TAMIS) and its results in terms of complete resections and complications possibly related to the procedure. **Materials and methods:** This is a series of TAMIS cases with prospective follow-ups. We analyzed the results of 27 patients who underwent the procedure at several centers in Medellín, Colombia, between January 2012 and December 2016. Twenty patients had Single Incision Laparoscopic Surgery while the GelPOINT path transanal access platform was used for the other six patients. Laparoscope optics provide support for 16 procedures while the more recently introduced flexible endoscope supported eleven procedures. **Results:** Twenty-seven TAMIS procedures were performed and evaluated. Ten patients were women (37%), and 17 were men. On average, patients were followed up for 32 months, but none less than 12 months. Average patient age was 68 years (52 to 83 years). The average tumor size was 5.3 cm (2 to 9 cm) and the average distance from the anal margin was 7 cm (5 to 9 cm). Postoperative complications occurred in six cases (22%). In one case, a rectal perforation was corrected laparoscopically during the procedure. Another perforation was corrected by the same transanal route. A rectal stenosis was managed with digital dilatation, there was one case of minor rectal bleeding, one case of urinary retention and one patient developed advanced rectal cancer with a positive microscopic margin (4%) three months after resection. There were no readmissions. There were no deaths due to the intervention. Pathology reported low grade adenomas in three cases (11%), high grade adenomas in 11 cases (41%), in-situ adenocarcinoma in six cases (22%), neuroendocrine tumors in five cases (19%), and one case each of cicatricial fibrosis (4%) and leiomyoma (4%). **Limitations:** The results cannot be extrapolated to the general population because of the limited number of interventions and performance of procedures by only two authors. **Conclusions:** Our initial experience shows TAMIS to be a minimally invasive procedure with low postoperative morbidity which is curative for benign lesions and for selected patients with early cancer.

Keywords

Rectal adenoma, early rectal cancer, minimally invasive transanal surgery TAMIS.

INTRODUCTION

Screening programs, better equipment and more trained personnel have resulted in detection of a greater number of rectal lesions and, in the case of neoplasms, at earlier stages. Lesions in their stages pose the dilemma of choosing local excision or a radical procedure. The first transanal excisions using the Parks technique and retractor were laborious and

limited to the distal 8 cm of the rectum. Since then microscopic, endoscopic and laparoscopic methods have modified transanal approaches. Still, many consider local excision to be sufficient for early lesions since it avoids the morbidity and mortality inherent in radical surgical procedures. (1, 2)

Transanal endoscopic microsurgery (TEM) is a minimally invasive technique originally conceived by Dr. Gerhard Buess in the 1980s to allow transmural resection of early rectal cancer (T1). (3) TEM reduces the rate of local recurrence below those of conventional transanal transanal excision, abdominoperineal resection (APR) and the Parks technique (4). TEM has less morbidity, shorter hospital stays, less postoperative pain during, and less patient time lost than does the Parks technique. (5)

The arrival of the transanal endoscopic operation (TEO) represented a new higher level of complexity with new equipment and instruments and a new learning curve. For this reason, it has been performed mostly by a small group of experts in high-tech centers. Although they have performed a large number of procedures, even after 30 years, and despite the benefits it offers to patients with benign and malignant tumors of the rectum, TEM/TEO is not used on a large scale. (6)

Since its introduction in 2009, (7) the TAMIS technique has been used with increasing frequency in Canada, the United States and Europe. (8-13) Recently, it has been presented in our country as an alternative to TEM for local resections of rectal tumors located in the middle and distal rectum. Initially, TAMIS became possible thanks to the development of the single port equipment and platforms for transanal surgery required by this technique. The use of a single transanal port device allows the use of conventional laparoscopic instruments, endoclamps and methods of advanced diverse coagulation (bipolar, harmonic, etc.).

Since its initial description, case reports and small series published about TAMIS have demonstrated that it is a technically possible and accessible alternative for most laparoscopic surgeons and has a lower initial cost than does TEM/TEO. In Latin America, the initial experiences with this method were published in Brazil by Alves et al. and Sevá-Pereira et al. although these authors included only 4 and 5 cases, respectively. (14, 15)

The purposes of this study are to show the initial local experience with TAMIS for lesions of the middle and lower rectum and to evaluate its feasibility, results and the safety of the intervention for at least one year following procedures.

MATERIALS AND METHODS

Prospective data about TAMIS treatment of patients with rectal lesions was collected from January 2012 to December 2016. Patients with diagnoses of adenomas or neuroendocrine tumors smaller than 2 cm were included, and patients with advanced rectal cancer were not included. As indicated in the National Comprehensive Cancer Network (NCCN) protocol, no routine MRI or CT scans were performed because of the conditions of T1 superficial lesions.

Two surgeons, Rodrigo Castaño and Juan Darío Puerta, performed all surgical procedures.

Mechanical intestinal preparation with enemas and prophylaxis with broad-spectrum antibiotics (second generation cephalosporins plus metronidazole) were performed prior to procedures. All surgery was performed under general anesthesia. In the first 12 procedures, patients were placed on the operating table in either lithotomy or jackknife surgical position depending whether the lesion's location was posterior or anterior. In the last 15 cases, patients were placed in lithotomy position, regardless of the location of the lesion.

The SILS™ Port platform (Covidien-Medtronic, Minneapolis, MN) was used for the first dozen cases. It is made of a special thermoplastic elastomer which allows atraumatic adaptation of the kit to the anal canal. After properly lubricating the kit and the anal canal, the port was installed. Subsequently, a pneumoperitoneum was established with CO_2 at a pressure of 12-15 mm Hg (Figure 1A and B).

The GelPOINT® Path was used for the last 6 cases. Recently introduced by Applied Medical (Rancho Santa Margarita, CA), it is specifically designed for performance of TAMIS. Its placement mechanics are similar to those of the SILS ™ Port platform (Figure 2A and B).

A 10 mm laparoscopic camera with a 30º angle was used in most cases, but in 10 cases an upper endoscope was used because of the ease of washing the lens and the possibility of aspirating the smoke resulting from dissection. In addition to the 10 mm optics port, two other 5 mm ports were used for manipulation of laparoscopic instruments such as tweezers, electrocautery spatula, hooks and scissors.

Dissection begins by marking the periphery of the lesion, leaving a margin of at least 2 to 3 mm outside the edge of the lesion (Figure 3A). Next, a cut is made to expose the submucosa and the lower margin of the lesion is lifted (Figure 3B). Then, electrosurgery (Figure 3C) is used to perform total thickness resection (Figure 3D), aiming to obtain lesion free, 0.5 cm deep, lateral margins. In 21 cases, wound closure (Figure 3E) was performed through a continuous primary suturing using V-Loc ™ (Covidien) or STRATAFIX™ (Ethicon) absorbable barbed sutures (Figure 3F).

Initially, all patients were hospitalized for one day. Those with more recent interventions and with small lesions were discharged the same day (except for patients with perforations whose hospital stay was 3 and 4 days). All immediate and late complications were recorded. All patients underwent rigorous follow-up at two, six and 36 weeks.

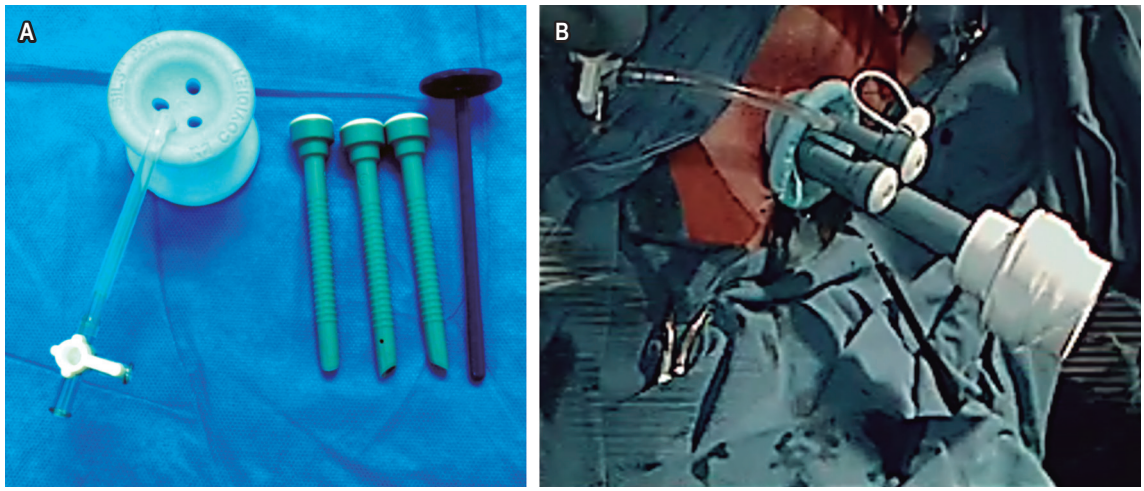

Figure 1. A. SILS™ Port and three 5 mm trocars. **B.** Introduction of the SILS ™ Port device.

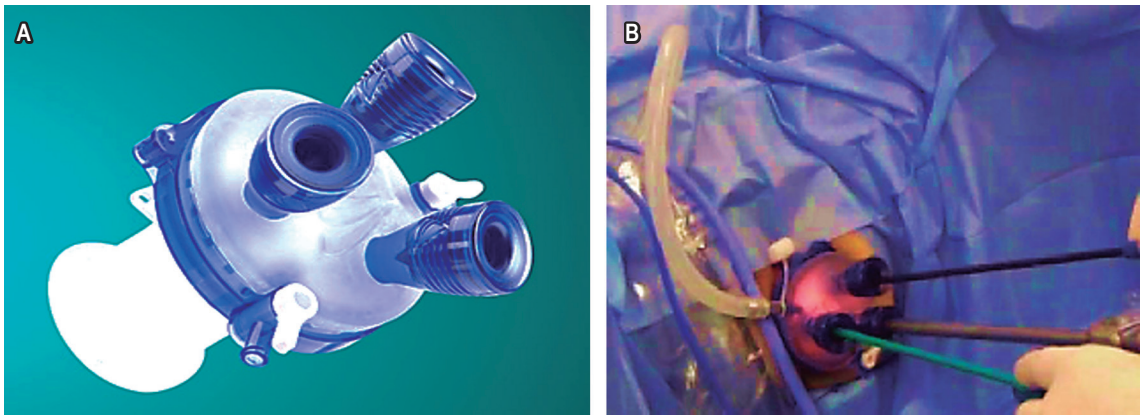

Figure 2. A. GelPOINT® Path transanal access platform. **B.** Location in the anal canal.

When there was a diagnosis of cancer including invasive carcinoma according to NCCN guidelines, patients were referred to cancer management. Each of these patients underwent total colonoscopies, evaluation of carcinoembryonic antigen (CEA) levels, an abdominal-pelvic MRI, and a CT chest scan.

The principal aims in each case were to evaluate the procedure's feasibility, the quality of the resected ion, and the patient's oncological prognosis. The feasibility of the procedure is defined as resection by TAMIS without recourse to a different transanal approach to complete the procedure. Good quality of resected segment is determined by the absence of fragmentation or a negative margin, defined as ≥1 mm of the tumor margin. Secondary objectives were to determine the clinical prognosis and perioperative morbidity and mortality, classified according to the Clavien-Dindo system.

RESULTS

TAMIS was performed successfully on 27 patients: 21 with SILS™ Port and six with GelPOINT® Path (22%). The lithotomy position was used in 24 cases, and the jackknife position was used in three cases (12%). Of the total patients, 10 were women (37%). The average age was 68 years (52-83 years) (Table 1).

The distance from the lower limit of the lesion to the anal margin determined by preoperative rigid rectoscopy was 7.1 (5-9) cm. The average surgical time was 115 (50-220) minutes. The average size of the lesions was 5.3 (2-9) cm. Resection of total thickness was achieved in all cases, and only two segments were fragmented (2 fragments).

The operative pathology reports showed low grade adenomas in three patients (11%), high grade adenomas in 11 patients (41%), pT1N0 adenocarcinomas in situ in

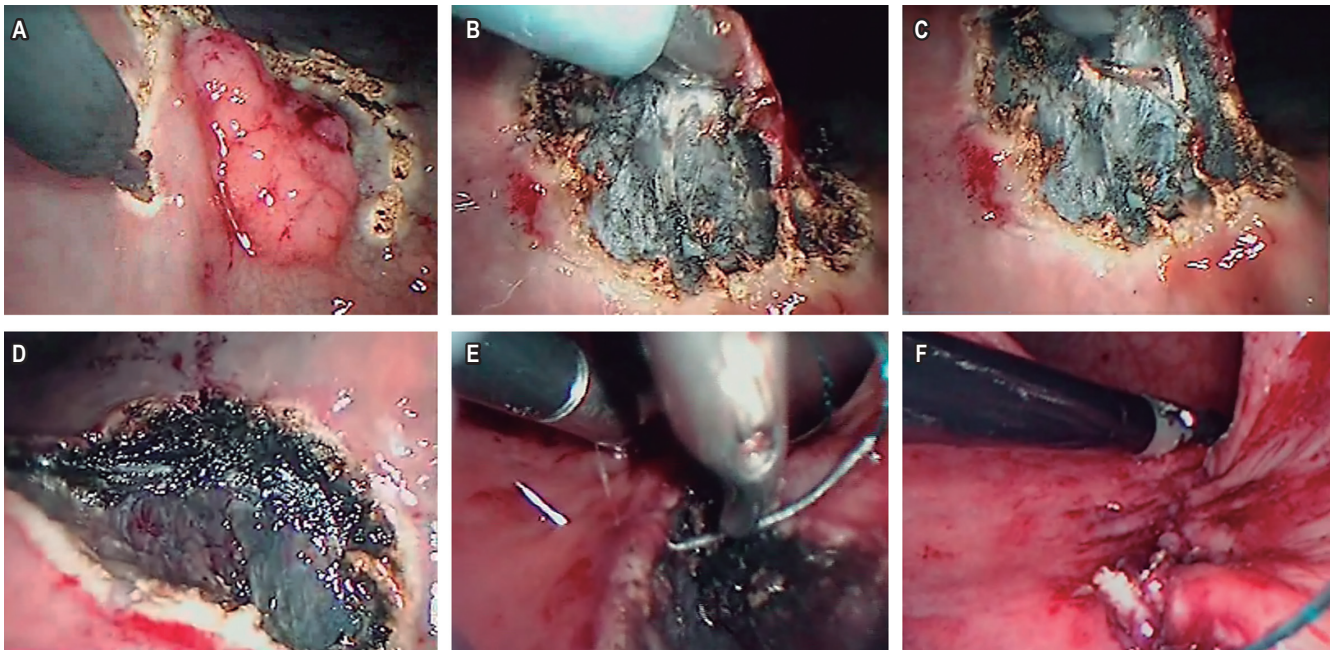

Figure 3. Sequence of events in the marking and resection of the total thickness of the rectal lesion. **A.** Marking the periphery of the lesion. **B.** Lifting lower margin. **C.** Transmural dissection of lesion. **D.** Complete excision of lesion. **E.** Suturing resection margins. **F.** Suture line with absorbable material.

Table 1. Characteristics of patients and lesions

n	Sex	Age	Distance from the anus (cm)	Size (cm)	Time (minutes)	Pathology	Complication	Months
1	F	63	7	3	210	HGD	No	57
2	M	65	8	2	220	NET	Perforation/laparoscopy	55
3	F	55	8	2	130	NET	No	54
4	M	52	6	4	105	HGD	Advanced cancer	17
5	M	78	6	3	130	HGD	No	50
6	M	83	8	3	105	LGD	No	48
7	F	60	7	4	120	CIS	No	46
8	M	71	6	3	125	HGD	No	43
9	M	67	8	2	100	NET	No	41
10	M	76	8	2	90	CIS	Perforation/suture	40
11	M	71	6	3	105	HGD	No	39
12	M	78	6	4	95	HGD	No	37
13	F	68	5	3	115	NET	No	35
14	M	81	8	6	110	HGD	No	33
15	F	68	5	8	100	LGD	Stenosis/dilation	30
16	M	74	7	8	120	HGD	No	29
17	M	72	7	7	130	HGD	No	27
18	F	53	6	7	145	CIS	No	26
19	M	68	7	3	90	Fibrosis	No	25
20	F	70	7	7	125	HGD	No	24
21	F	74	8	6	105	CIS	No	23
22	M	68	7	3	90	NET	No	21
23	M	70	8	3	80	NET	No	21
24	F	66	7	5	100	HGD	Bleeding	20
25	M	61	9	6	80	CIS	Urinary retention	19
26	F	59	8	3	50	HGD	No	17
27	M	68	7	5	110	Leiomyoma	No	12

CIS: carcinoma in situ; HGD: high grade dysplasia; LGD: low grade dysplasia; NET: neuroendocrine tumor.

six (22%) cases, neuroendocrine tumors in five patients (18%), one case of local fibrosis (4%), and one case of leiomyoma (4%).

All tumors, except one (4%), were resected with negative microscopic resection margins. The extension studies of the patient in question showed extensive local, regional and distant compromises from interval colorectal cancer (I-CRC). Eighteen 18 months earlier, a colonoscopy's results were negative for a tumor in the rectum.

Wounds were not closed in five cases (18%). These patients evolved without major developments similar to those whose wounds were closed. There was bleeding from only one of the wounds that was left open without suturing.

Two rectal perforations (8%) occurred: one in the second patient of the series, and the other in the 10th patient of the series. The first was corrected laparoscopically. The second perforation, which accessed the peritoneal cavity, was corrected by transanal suturing. There were no subsequent adverse events in the evolution of these patients.

Postoperative bleeding occurred and there were no infectious complications. No patient had to be reoperated. There was no mortality associated with the technique. The average duration of hospitalization was 1.1 days. The patients had no recurrence of lesions during average follow-up time of 33 months.

DISCUSSION

By the middle of the first decade of this century, minimally invasive surgery pointed to an innovation: natural orifice transluminal endoscopic surgery (NOTES). (16) This route reduces traumatic access through the abdominal wall and looked like it might make it possible to dispense with it completely. This led to the appearance of multi-port laparoscopic access through the navel in so-called single-port surgery. (17) This stimulated the development and implementation of TAMIS, the concept, technique and initial prognosis of which was reported by Atallah et al. (7) It has since been validated by several authors from different medical centers. (18, 19)

Management of benign and malignant rectal tumors depends on a healthy balance between curative intent and preservation of functionality. TAMIS is a new platform for local resection of benign rectal lesions with malignant potential as well as well selected malignant lesions. Initial encouraging results have led significant increases in its use. (13) In this study, we report the first 27 cases of TAMIS performed for the treatment of premalignant or malignant rectal lesions. In all cases, it was possible to completely resect the rectal lesion without significant morbidity. This is true despite two perforations which entered the peritoneal cavity, but both were quickly corrected: the first by laparoscopy, and the second by direct suturing.

Transanal surgery was first performed with the Parks technique and had more recently been performed with the microscopic approach. Nevertheless, a number of authors consider TEM/TEO to have a significant degree of technical difficulty. (6) Fifteen years since the advent of this technique, the number of procedures performed by Buess had not exceeded 500. (20) Among the reasons for its limited use by expert surgeons were the initial investment associated with equipment acquisition, the need for special training, and the small sample of patients who benefit from the method. In contrast, only four years after the introduction of TAMIS, there are already reports of it being performed from 16 countries. (1)

The evidence shows that, for selected patients with adenocarcinoma pT1N0, local resection with endoscopic microsurgery has rates of recurrence and survival similar to radical resections. In 2012, Lezoche et al. demonstrated that, in patients with cT2N0 rectal adenocarcinomas who received neoadjuvant treatment, an endoscopic microsurgery resection could be performed with results similar to those of total mesorectal resection in terms of recurrence and survival. (21) The indications for TAMIS are the same as those for TEM/TEO.

Until the last decade, the TEM and TEO platforms were the only ways to perform an endoscopic transanal resection. However, TEM and TEO are not available in many hospitals, and TAMIS has emerged as an advanced alternative with greater cost-effectiveness and with results that could be better than those of TEM/TEO in the future. This has already allowed for performance of minimally invasive treatment of rectal tumors at more medical centers. (2) In the United States, the cost of the ports required for the TAMIS platform is between $500.00 and $650.00, equivalent to the cost of materials used for CO2 insufflation with a TEM platform. (10)

Room preparation for the procedure is quick, and it offers a 360 degree view rather than 220 degree view inside the rectal lumen. Moreover, conventional laparoscopic instruments are used. These advantages of TAMIS over TEM/TEO. In addition, patient placement is versatile and patients can be placed in the lithotomy position in all cases of TAMIS, which is an additional advantage.

Finally, TAMIS' port diameter is only 30mm, 10 mm smaller than the TEM/TEO port. Due to TAMIS' port design, dilation is safe and non-traumatic. In contrast, the TEM port is rigid, and it has been associated with anorectal dysfunction in prospective studies. Dysfunction has included reduction in resting pressure and decreases in voluntary contraction found at six week follow-up examinations.

It is possible that sphincters dilate less during TAMIS than during TEM/TEO. (22) In 2014, Schiphorst et al. evaluated the functioning of the anal sphincter before and after performing TAMIS and found no manometric alterations. In addition, they found improvement in the fecal incontinence severity indexes of 37 patients who had undergone surgery thus demonstrating improvement in anorectal function after TAMIS. Of the 17 patients who had incontinence before surgery, fifteen improved, one remained the same, and the other worsened. (23)

One of the main technical difficulties of TAMIS is occasional instability of insufflation which can lead to intermittent collapse of the rectal lumen thus hindering surgery. This event can be resolved, to a greater or lesser degree, by increasing pressure to 15-20 mm Hg, by greater relaxation, or by repositioning the port. As with TEM/TEO, another difficulty is related to release of smoke from electrocautery. The SILS ™ Port system's 3 ports are all used by optical devices and surgical instruments, but the GelPOINT® Path has a special port expressly for smoke removal.

With respect to the technique's limitations, one has established the importance of a support endoscope support to facilitate smoke aspiration, to allow lens washing, and to add pressure to maintain insufflation. With the retroversion, visual control of the proximal limit of the lesion and passage of the instruments through the working channel is facilitated. This has shown encouraging results in terms of the execution time and minor complications. (24, 25) More recent descriptions combine submucosal endoscopic dissection with TAMIS to treat lesions of the lower rectum that compromise the dentate line. (26, 27)

Once the lesion has been removed, the dilemma of whether or not to close the rectal wound is raised. Some publications have described infectious complications such as abscesses after the closure of the wound. (28) A metaanalysis published in 2017 by Menahem et al. showed that there are no differences in terms of infection and reinterventions between patients whose wounds have been closed and those whose wounds have remained open. Another metaanalysis published by Lee et al. in 2018 suggests a higher incidence of clinically significant hemorrhaging in patients with open wounds (9% vs. 3%, p = 0.045). (29, 30) In our study, wounds of 21 patients (81%) were closed. The tendency is to leave wider wounds open, and we only left the largest wounds open. They evolved with stenoses which were successfully managed with digital dilations.

In this study, positive margins were only observed on one resected specimen. This patient's evolution was unexpected with extensive liver, lung and local and regional metastases from interval colorectal cancer. Pathological analysis showed tissue removed was fibrotic in only one case. In two cases, the specimen had fragmented, but the margins were not compromised, and there were no effects on patient evolution.

Increasing, reports of TAMIS with multiple disposable ports designed for single-port surgery are being published although this is still under evaluation.

Several issues need clarification including the viability of endoscopic transanal access for upper rectal procedures since the TAMIS platform does not include surgical rectoscopy. Its addition could theoretically provide stability to the surgical procedure at these sites.

In two cases, perforations that entered the peritoneal cavity occurred during surgery. The first was corrected with the support of laparoscopy performed by the authors while the second wound was properly closed using TAMIS. The data reveal that perforations of the rectum do not compromise the clinical or oncological prognoses of these patients. (31, 32) Perforation of the rectum during removal of the complete thickness increases surgery time and causes minimal abdominal trauma but does not increase morbidity.

A study of 254 TAMIS procedures published in 2018 found that overall rate of positive margins (resection R1) was 7%, with an indication of malignancy of 57%. In TEM, an R1 rate of 10% is accepted, and in transanal resection the accepted rate is 26%. The authors conclude that TAMIS is a complex procedure that requires a minimum of 14 to 24 cases to achieve an acceptable R1 resection rate, shorter duration of surgery, and improvement in the diameters of resected lesions. (33)

One of the limitations of these studies, including ours, is absence of quality of life evaluations. Fecal continence was not evaluated, although there are questionnaires such as the Fecal Incontinence Severity Index and the EuroQolEQ-5D. The latter has shown a better quality of life after TAMIS, presumably secondary to tumor removal. (34) The aforementioned questionnaires are easy for patients to use, are excellent tools for assessing anorectal function over time, (20) and can be incorporated into routine clinical follow-up in our center. Another limitation of these studies is the bias inherent in retrospective analyses due to lack of data in medical records. In contrast, our clinical and surgical data were complete since the data was collected prospectively. Sometimes, pathological records do not contain tumor dimensions, but margin analyses were well described. Finally, it is important to keep in mind that TAMIS is an evolving surgical technique and that samples in the published series are small so surgical results are subject to variations from center to center (Table 2).

One limitation of this study is its retrospective nature, which can induce some selection biases and affect the veracity of conclusions. Another is the fact that it concentrates on procedures performed by two of the authors at a referral

Table 2. Comparisons between results of this study and series with more than 20 patients

Author	Year	n	Port	B:M:O	Surgery	Complications	R1	Relapse	Months
Ragupathi (35)	2012	20	SILS™ Port	14:6	0	1	1	1	ND
Cantero (24)	2012	20	SILS™ Port	0:20	0	0	ND	ND	ND
Albert (9)	2013	50	SILS™ Port -GelPOINT® Path	25:23	0	4	3	2	20
Lee (36)	2013	25	SILS™ Port	6:9	0	1	0	0	10
McLemore (10)	2014	32	SILS™ Port -GelPOINT® Path	13:16	3	5	0	0	3-23
Hanhloser (37)	2014	75	SILS™ Port	25:49	3	23	3	ND	ND
Gill (38)	2015	32	GelPOINT® Path	11:16	0	16	0	1	ND
Sumrien (39)	2016	28	SILS™ Port -GelPOINT® Path	17:11	2	7	6	2	ND
Haugvik (18)	2016	51	SILS™ Port -GelPOINT® Path	43:8	0	6	11	0	48
Verseveld (34)	2016	24	SILS™ Port	4:20	0	1	0	0	ND
Quaresima (40)	2016	31	SILS™ Port -GelPOINT® Path	10:17	0	8	1	1	30
Keller (41)	2016	75	SILS™ Port -GelPOINT® Path	55:17:4	3	5	5	1	36
García-Flórez (42)	2017	32	GelPOINT® Path	15:14:3	0	8	1	0	40
Caycedo-Marulanda (13)	2017	50	GelPOINT® Path	23:17:10	0	0	8	4	21
Castaño & Puerta	2018	26	SILS™ Port -GelPOINT® Path	14:12	1	5	1	0	33

B:M:O: benign, malignant, others; R1: positive margin; ND: no data.

institution. Consequently, this experience cannot be generalized to all surgeons. Also, average follow-up time was less than three years. This is a short time although most relapses have occurred in the first two years and are related to tumor biology rather than the quality of resection. (43) It is not clear if the absence of relapses in our series is due to the short follow-up time. Functional results were not evaluated, however, the results are encouraging with respect to absence of compromised anorectal function related to the procedure. Frequently, this function improved with removal of the rectal lesion.

In conclusion, consistent with current evidence supporting TAMIS as a viable alternative to radical excision of the rectum and showing that it produces less morbidity with faster recovery times and possible cost savings, our figures suggest that TAMIS is safe, effective and reproducible. In addition, we anticipate increasing use of this technique for more complex colorectal surgeries in our center, and we emphasize the value of histological evaluation of the resected segments.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Differential characteristics of autoimmune hepatitis in Colombian older adults: a cohort study

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Abstract

Introduction: Elderly patients with autoimmune hepatitis (AIH) are a special population because of predisposition mediated by the human leukocyte antigen (HLA) system. An indolent and progressive course of the disease has been described. No data are known for the Latin American population. **Objectives:** This study compares clinical presentations, diagnoses, treatments, responses to treatment and course of disease for AIH patients who are over 65 years of age with those of AIH patients who are under 65. **Methods:** This is a retrospective cohort study of patients with HAI evaluated between January 2010 and December 2016. Statistical analyses used SPSS version 20.1. **Results:** Two hundred fourteen patients were included. Elderly patients had hypertension (34.5% vs 15.1%, p = 0.011), dyslipidemia (20.7% vs 5.9%, p = 0.006) and cardiovascular disease (17.2% vs 2.7%, p = 0.001) more frequently than did the younger patients. In addition, the elderly had a higher frequency of cirrhosis confirmed histologically and radiologically (55.1% vs. 33.5%, p = 0.024) at the time of diagnosis. Older patients had a higher rate of biochemical remission resulting from treatment (100% vs 83.9%, p = 0.022). There were no differences in hepatic analyses, autoantibodies, type of pharmacological treatment received, relapses, adverse effects related to treatment, requirements for liver transplantation and deaths. **Conclusion:** AIH affects the Colombian adult population at all ages and should be considered in the diagnostic approach of elderly patients who have liver disease because this group has a higher frequency of cirrhosis at the time of diagnosis. Early diagnosis is important because treatment is effective and well tolerated.

Keywords

Autoimmune hepatitis, Latin America, elderly patients.

INTRODUCTION

Since its first description in 1950, autoimmune hepatitis (AIH) has been considered to be a disease of young women. (1) Recent subsequent studies have found a bimodal behavior with peaks of occurrence between 10 and 30 years and between 40 and 50 years although it can affect people of all age groups. (2-5) AIH is an important cause of acute liver failure, liver cirrhosis, and morbidity and mortality. It can require liver transplantation and result in post-transplantation liver dysfunction. (6)

Older AIH patients are a special population for several reasons. (7) First, studies differ about whether the cut-off age for considering patients as older adults should be 60 or 65 years old. Second, there may be genetic predisposition in this age group due to higher prevalences of HLA-DR4 and HLA-DRB1*04. (5, 8) Third, these patients are a diagnostic challenge because the condition is diagnosed later than in the younger population, and because there is a higher frequency of asymptomatic and cirrhotic patients at the time of diagnosis (5, 8, 9, 10) Similar remission rates in response to immunosuppressive treatment have been reported with fewer relapses after treatment ends but with a greater frequency of intolerance and related adverse effects. (5, 10, 11) The course of AIH in the older population is usually indolent and progressive and can

be masked by the presence of other diseases, especially autoimmune diseases. (11)

The existing information on the differential behavior of AIH in older adults comes from retrospective studies conducted in the North American (8), European (4, 10, 12-14) and Asian populations as well as from systematic reviews of the literature. (5, 15) Prior to this study, there had been no published data on this group of patients in Latin America.

The objective of this study is to compare differences in the clinical and diagnostic characteristics, treatments, and responses to treatments, course of disease, and prognoses of two groups of AIH patients, those younger than 65 years and those older than 65.

MATERIALS AND METHODS

Design and Sample

Sampling for this retrospective study of a historical cohort was based on diagnoses of AIH (International Classification of Diseases 10 code K75.4) in the records of the medical histories of patients treated in the emergency, hospital inpatient, and outpatient services of Hospital Pablo Tobón Uribe (HPTU) in Medellín, Colombia from January 2010 to December 2016. A sample size was not estimated because all patients diagnosed with AIH and treated during the study period were included.

Population

Patients were included if they were 16 years or older and had been diagnosed with AIH according to the simplified diagnostic criteria published in 2008 by the International Autoimmune Hepatitis Group (IAIHG) and had a score of less than six for which the response to drug treatment could help confirm the diagnosis. (2, 17)

Patients diagnosed before age 16, those with overlap syndromes of AIH with either primary biliary cholangitis (AIH-PBC) or primary sclerosing cholangitis (AIH-PSC), patients with acute liver failure due to AIH and those with drug induced AIH were excluded. Similarly, patients with absence of clinical, biochemical or histological data were excluded if lack of data preventeed adequate diagnosis.

Variables

Data were collected from the diagnosis of AIH to the last clinical follow-up review in the electronic records of the hospital's medical history and using a previously designed collection form.

Sociodemographic variables collected included age at the time of diagnosis of AIH, sex, and race. Comorbidities including other autoimmune diseases and clinical variables such as the form of presentation were registered. Presentations were classified as follows:

- Asymptomatic: those with a biochemical alteration liver without symptoms
- Non-specific symptoms: those with biochemical alteration of the liver
- Specific symptoms such as asthenia, hyporexia and fever, acute hepatitis
- Acute hepatitis: those with abdominal pain, nausea, fever and jaundice associated with transaminases at least 3 times the upper limit of normal but without meeting the criteria of acute liver failure
- Liver cirrhosis (those diagnosed by biopsy, clinically or through imagining.

Laboratory variables recorded were measured at the time of diagnosis and during follow-up to evaluate the response to treatment. They included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, serum albumin, and serum immunoglobulin G (IgG) levels plus prothrombin time and the International Normalized Ratios (INR). In addition, the titers of antinuclear autoantibodies (ANAs), anti-smooth muscle antibodies (ASMAs) and antimitochondrial antibodies (AMAs) were registered.

Histological characteristics were classified according to the recommendations for AIH diagnosis of the IAIHG as either

- *Typical of AIH*: interface hepatitis, lymphocytic or plasmocytic infiltrates in portal spaces with extension to the lobule, emperipolesis and formation of rosettes, or
- *Compatible with AIH*: chronic hepatitis with lymphocytic infiltrate without the other typical findings of autoimmune hepatitis. (16)

The degree of liver fibrosis was evaluated according to the METAVIR scale of grades F0 to F4, where F0 represents the absence of fibrosis and F4 represents advanced fibrosis with cirrhosis.

The induction and maintenance pharmacological treatment scheme used by the hepatology group was evaluated. During the induction phase of the scheme patients receive 0.5-1 mg/kg/day of prednisolone and 1 mg/kg/day of azathioprine. Subsequently, the dose of prednisolone is gradually decreased over three months, and the dose of azathioprine is progressively increased up to 2 mg/kg/day, depending on tolerance and response to treatment during the maintenance phase. The following categories were established for evaluation of treatment response:

- Biochemical remission: normalization of transaminases and IgG

- Partial clinical improvement and transaminase response but without normalization
- Therapeutic failure: failure to achieve at least a 25% decrease of transaminase levels below start of treatment level
- Relapse: reelevation of ALT to more than three times the upper limit of normal according to the IAIHG criteria, an increase in IgG levels, or a worsening of histological findings after having achieved remission through drug treatment. (2)

Follow-up was carried out until the last clinical evaluation. During this period complications were encountered. They included the development of cirrhosis in patients who had not previously had cirrhosis, requirement of liver transplantation (Our group considers this option in patients 65 and younger and in selected cases over 65.), post-transplant recurrences, liver retransplantation and death.

Ethical Issues

The study is within the parameters of the Helsinki Declaration of 2013 for studies with human beings and within the regulation on clinical research in Colombia (Resolution 008430 of 1993). In addition, it was approved by the HPTU ethics committee. Finally, the final manuscript adhered to the recommendations Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for reporting observational studies. (18)

Statistical Analysis

Statistical analysis was performed with SPSS version 20.1 (SPSS Inc.). Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented as means and standard deviations for normal distributions and as interquartile ranges (IQR) for distributions that are abnormal according to the Kolmogorov-Smirnov test. The differences between groups were established with the χ^2 test for categorical variables and the Mann-Whitney U test for differences of medians. Values of p were calculated in two tails, where $p < 0.05$ represents a statistical significance.

RESULTS

A total of 214 patients met the inclusion criteria. Of these, 185 were diagnosed with AIH before the age of 65, and 29 were diagnosed with AIH at or after the age of 65. Eighty-three patients were excluded for a variety of causes (Figure 1). The age distribution at the time of AIH diagnosis is shown in Figure 2.

Most patients in both groups were women. There was a statistically significant difference in the median follow-up time after diagnosis of AIH. It was 50 months for the under-65 group but only 19 for the over-65 group ($p < 0.001$) (Table 1).

Clinical Issues

In both groups, the most frequent comorbidity was hypothyroidism. There were no differences in other autoim-

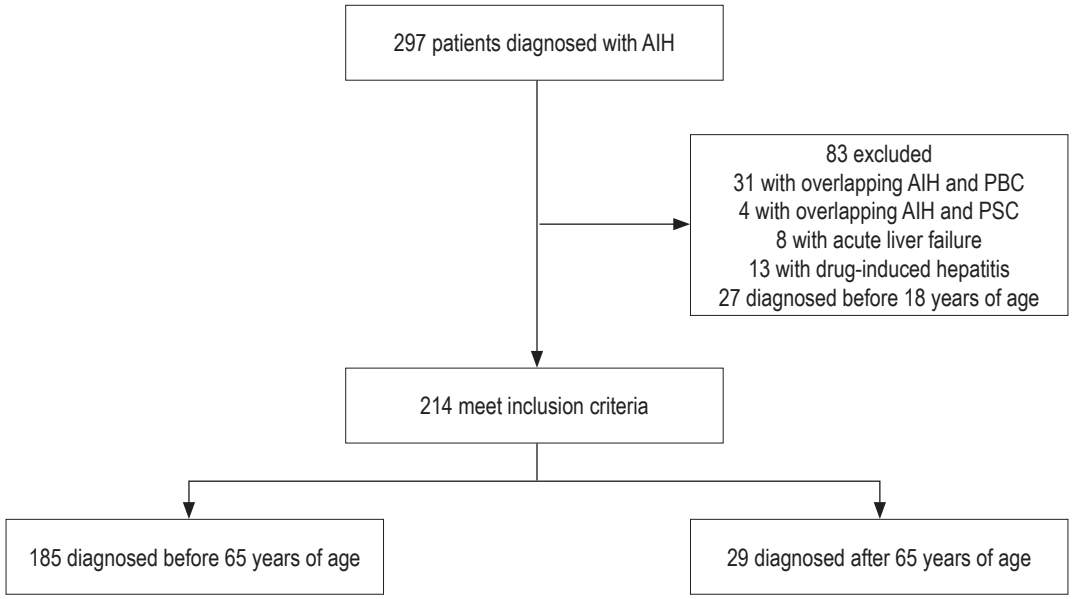

Figure 1. Study flow chart. AIH: autoimmune hepatitis; AIH-PBC: autoimmune hepatitis- primary biliary cholangitis; AIH-PSC: autoimmune hepatitis-primary sclerosing cholangitis.

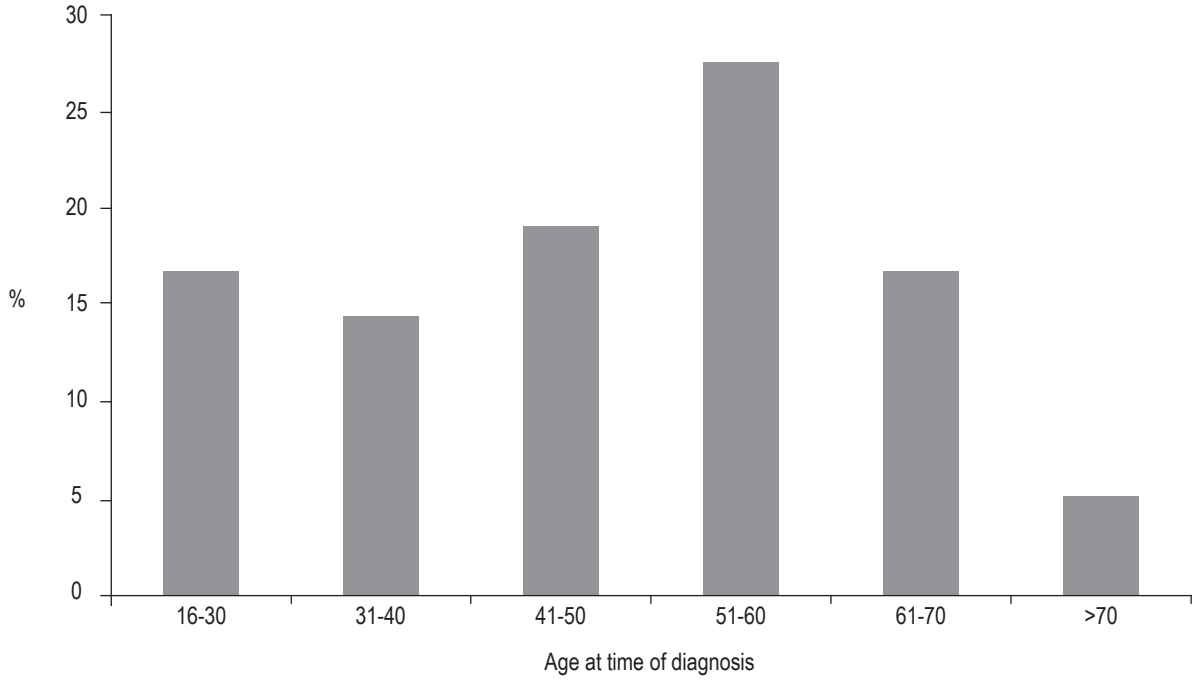

Figure 2. Age distribution at the time of AIH diagnosis.

mune diseases. Differences with statistical significance were found for arterial hypertension (15.1% vs. 34.5%, p = 0.011), dyslipidemia (5.9% vs. 20.7%, p = 0.006) and cardiovascular disease (2.7% versus 17.2%, p = 0.001). These comorbidities were frequent in patients diagnosed with AIH at or after 65 years of age. The main form of clinical presentation in both groups was acute hepatitis. Of the patients with acute hepatitis 27.5% were already cirrhotic (acute hepatitis on cirrhotic liver). For under-65 patients this proportion was 26.6% while in the older group it was 33.3%.

In total, 21% of the younger group and 31% of the older group were clinically cirrhotic at the time of diagnosis, but this difference was not significant. Nevertheless, evaluation if the degree of fibrosis by imaging and liver biopsies found a higher frequency of cirrhosis at the time of diagnosis in older patients (33.5% vs. 55.1%, p = 0.024).

Laboratory Findings

There were no differences in the biochemical parameters or autoantibody profiles between the two groups (Table 1). Diagnose of 82% of the patients in both groups were histologically confirmed. More than 95% of cases were either typical of AIH or compatible with AIH, and there were simplified scores of probable or definitive AIH in more than 80% of the patients. There were no significant differences in the distribution of the degree of hepatic fibrosis on the METAVIR scale, but there was a higher frequency of F4 fibrosis in the group of older patients (39.9% versus 58.3%, p = 0.089).

Treatment, Response and Evolution

The combination of a steroid and an immunomodulator was the most frequently administered treatment in both groups. As shown in Table 2, there were no significant differences between the groups. The group of older patients had a higher frequency of biochemical remission with treatment (83.9% versus 100%, p = 0.022) which allowed more frequent suspension of steroid treatment, although this was not statistically significant. Similarly, older patients had a lower, but not statistically significant, frequency of relapses during treatment. In 3.2% of the younger group, immunosuppressive therapy was completely discontinued. In both groups, there were no differences regarding the development of AIH during follow-up among patients who were not cirrhotic at the time of diagnosis. In total, 13 patients underwent transplantation. Of these, only one was from the group of older patients. She was diagnosed with cirrhosis at age 66. Liver transplantation was indicated due to complications related to portal hypertension. There were no differences in requirements of liver transplantation,

Table 1. Demographic, clinical, serological and histological characteristics of patients with AIH according to age.

	Patients under 65 years of age n=185	Patients over 65 years of age n=29	*p*
Women n (%)	167 (90.3)	28 (96.5)	0.269
Age at diagnosis, median in years (IQR	47 (35-56)	71 (66-74.5)	<0.001
Follow-up time in months, median (IQR)	50 (17-80.5)	19 (5.5-37.5)	0.003
Autoimmune comorbidity - n (%)	56 (30.3)	9 (31)	0.934
Comorbidities - n (%)			
Hypothyroidism	50 (30.8)	13 (44.8)	0.135
Hypertension	28 (15.1)	10 (34.5)	0.011
Dyslipidemia	11 (5.9)	6 (20.7)	0.006
Cardiovascular disease*	5 (2.7)	5 (17.2)	0.001
Diabetes mellitus	15 (8.1)	4 (13.8)	0.317
Obesity	7 (3.8)	0 (0)	0.284
Chronic kidney disease	1 (0.5)	1 (3.4)	0.130
Clinical presentation - n (%)			
Asymptomatic, hepatic biochemical alteration	34 (18.4)	5 (17.2)	0.883
Non-specific symptoms	37 (20)	5 (17.2)	0.728
Acute hepatitis	60 (32.4)	9 (31)	0.881
Liver cirrhosis	39 (21.1)	9 (31)	0.232
No data	15 (8.1)	1 (3.5)	0.375
AST, median U/L (IQR)	226 (99-718)	313 (178-727)	0.770
ALT, median U/L (IQR)	260 (95-698)	222 (105-705)	0.678
Alkaline phosphatase, medium U/L (IQR)	178 (116-297)	170 (138-278)	0.827
Diagnosis IgG levels, median mg/dL (IQR)	2000 (1700-2501)	1863 (1485-2800)	0.661
Positive ANA ≥1: 40 - n (%)	142 (76.8)	24 (82.8)	0.471
Positive ASMA ≥1: 40 - n (%)	57 (30.8)	13 (44.8)	0.135
AMA positive - n (%)	12 (6.4)	0 (0)	0.158
Liver biopsy - n (%)	153 (82.7)	24 (82.8)	0.994
Liver fibrosis at diagnosis - n (%)¶			
F0-F1	18 (11.8)	3 (12.5)	0.918
F2-F3	42 (27.4)	5 (20.8)	0.495
F4	61 (39.9)	14 (58.3)	0.089
No data	32 (20.9)	2 (8.3)	0.146
Cirrhosis diagnosed clinically and by laboratory tests, imaging and biopsy	62 (33.5)	16 (55.1)	0.024
Biopsy finding - n (%)£			
Compatible with AIH	48 (31.4)	4 (16.6)	0.141
Typical of AIH	105 (68.6)	20 (83.4)	0.141
AIH diagnostic score - n (%)£			
<6 points	36 (19.4)	3 (10.3)	0.237
6 points	56 (30.3)	13 (44.8)	0.119
> 6 points	93 (50.3)	13 (44.8)	0.586

ALT: alanine aminotransferase; AMA: antimitochondrial antibodies; ANA: antinuclear antibodies; ASMA: anti-smooth muscle antibody; AST: aspartate aminotransferase; AIH: autoimmune hepatitis; IgG: immunoglobulin G; IQR: interquartile range

* Ischemic heart disease, heart failure, peripheral arterial disease, stroke.

¶ Percentage calculated on patients with liver biopsy in each group.

£ According to IAIHG recommendations in Hennes EM et al. Hepatology 2008 Jul; 48 (1): 169-76.

Table 2. Treatment characteristics, response to treatment and evolution over time.

	Patients under 65 years of age n=185	Patients over 65 years of age n=29	Valor de *p*
Treatment - n (%)			
Steroid	11 (6)	2 (6.9)	0.842
Steroid + immunomodulator	118 (63.8)	20 (69)	0.588
Immunomodulator, steroid suspension	33 (17.8)	6 (20.7)	0.711
Suspension of treatment	6 (3.2)	0 (0)	0.327
None	10 (5.4)	1 (3.4)	0.657
No data	7 (3.8)	0 (0)	0.284
Response to treatment - n (%)*			
Biochemical remission	141 (83.9)	28 (100)	0.022
Partial remission	20 (11.9)	0 (0)	0.053
Therapeutic failure	5 (3)	0 (0)	0.357
No data	2 (1.2)	0 (0)	0.561
Relapse - n (%)*	35 (18.9)	2 (6.9)	0.111
Development of cirrhosis during follow-up - n (%)¶	18 (14.6)	2 (16.6)	0.873
Liver transplant - n (%)	12 (6.5)	1 (3.4)	0.522
Post-transplant recurrence - n (%)£	2 (16.6)	1 (100)	0.057
Replantation - n (%)	1 (8.3)	0 (0)	0.764
Death - n (%)	10 (5.4)	0 (0)	0.200

* Percentage calculated on the total of patients who received treatment in each group.
¶ Percentage calculated on the total of non-cirrhotic patients at the time of diagnosis of AIH in each group.
£ Percentage calculated on the total number of patients with liver transplantation in each group.

recurrence of AIH post-transplant, liver retransplantation or mortality.

DISCUSSION

Globally, reports on the differential characteristics of AIH in older patients are scarce, retrospective and heterogeneous. Two different cut-off ages, 60 and 65, have been used to define older patients. The North American, European and Asian patient populations have received the most study, (5) but no data on the Latin American population has been published.

In total, there are 10 studies that evaluate the behavior of AIH in this group of patients. These have recently been analyzed in a systematic review of the literature. (5) Our study is the first that describes the differential behavior of AIH in older Latin American adults who constitute a non-negligible percentage of the total number of patients with AIH: 12.9% (29 of 224) in this study and 10.4 % (29 of 278) of the population of patients with AIH recently published by our group. (19) Both percentages are much lower than those reported globally (24.8%). (5) However, these differences may have several explanations. First, there is the small number of patients reported worldwide: in total 264 older patients with AIH. Second, the heterogeneity of the populations studied, different inclusion criteria, and different cut-off ages. Three studies had a cut-off age of 60 years and seven studies had a cut-off age of 65 years. (5) We used the 65-year-old cut-off age since it was used in most of the reported studies. Third, this definition plus our study's exclusion of patients under 18 years of age may affect our comparisons. Moreover, we included some patients who had not had liver biopsies (20.9 %), and we used simplified AIH scores of less than six points (17.4%) with the response to treatment confirming the diagnosis of AIH. (2, 17) We also excluded patients with AIH-PBC and AIH-PSCE overlap syndromes, medication-induced AIH and acute liver failure due to AIH for which different courses and prognoses have been described. (3, 20-22)

The predominance of women in both age groups and bimodal behavior of AIH in terms of age was corroborated by this study. (2) It should be noted that 22% of the

patients were diagnosed after the age of 60 which reinforces the importance of taking into account AIH as a cause of liver disease in this age group. This percentage was similar to that reported in other studies (20%). (4, 8, 9)

Although there were no differences of clinical presentation between the groups, it is important to highlight that almost one fifth of the patients were asymptomatic, since it has been found that up to 26% of patients who do not have symptoms are cirrhotic at moment of diagnosis of AIH. (23) AIH should be considered in differential diagnosis whenever alteration of the biochemical-hepatic profile is found in adults, regardless of the patient's age. (2, 11)

A relevant finding of this study is that older adults had a greater degree of liver fibrosis at the time of the diagnosis of AIH than did younger AIH patients, although this difference was not significant in terms of F4 fibrosis found by liver biopsy (58.3% versus 39.9%, p = 0.089). It was significant when cirrhosis was assessed by clinical symptoms of ascites, collateral circulation, encephalopathy, gynecomastia, and telangiectasias combined with analytical tests (hypoalbuminemia, thrombocytopenia, prolonged coagulation times), imaging and biopsies (55.1% versus 33.5%, p = 0.0024). This is consistent with reports from other populations elsewhere in the world. (5) This suggests an indolent course of AIH in older people which could be explained by several reasons. According to Czaja, (7) the subclinical course of the disease can lead to delayed diagnosis and greater prevalence of comorbidities such as arterial hypertension, cardiovascular disease, osteoporosis and neoplasms. (10,11) This suggest an alternative diagnosis that conditions the use of corticosteroids for treating AIH. In addition, there is greater frequency of autoimmune comorbidities in patients with HLA-DRB1*04 which can mask liver manifestations. (8) In this study, there were significant differences found in presence of arterial hypertension, dyslipidemia and cardiovascular disease in the older population which did not impact the type of treatment received for AIH for which no differences were found. No differences were found with respect to autoimmune comorbidities.

Aging involves a series of changes which alter homeostasis of the immune response and which can influence the presentation and course of autoimmune diseases. (24) Classic extrahepatic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome have been studied most. (24) Beyond the immunosenescence process, changes have been found in the architecture of organs involved in the immune response, alterations in the balance between proinflammatory and anti-inflammatory factors, and in the balance between pro-apoptotic and anti-apoptotic factors all of which can modify both humoral and cellular immune responses. (24, 26, 27) In older people, greater thymic atrophy has been reported with a decrease in the immune response mediated by T lymphocytes without affecting the humoral response. (27, 28) This could explain the findings of hyperglobulinemia, better response to immunosuppressive treatment, (11) and lower relapse frequency, (5) the latter two of which were corroborated in this study (100% biochemical remission versus 83.9%, p = 0.022). The indications and treatment scheme recommended for AIH in the older population do not differ from those for the general population. (2) However, treatment may be conditioned by comorbidities and a higher frequency of adverse effects. (7, 9) It should be noted that we found no differences in the development of adverse effects related to treatment in our population.

This study has several limitations starting with those inherent in a retrospective study, especially information bias, since the data were collected from the hospital's electronic medical record base. Second, this is a single-center study. However, this is a national referral center for liver diseases which has the largest number of patients with AIH published in Latin America. (19) Third, some patients were included without liver biopsies who had been diagnosed with a simplified AIH score of less than six. However, these patients responded to pharmacological treatment which helped to corroborate these diagnoses. Fourth, HLA haplotypes were not characterized even though HLA-DQ2 and HLA-DR2 have been demonstrated to be risk factors for AIH in the Latin American population, (29) and even though HLA-DR4 and HLA- DRB1*04 have been demonstrated to be risk factors for older patients. (5, 8) Finally, there were differences in patient follow-up times which were shorter for the older group. This limitation has also been found in the most representative studies of AIH in older adults by Al-Chalabi et al. and by Czaja et al. (4, 8) In our study, this is explained by growing awareness in recent years of the need to search for AIH in older patients: 72.4% of these patients were diagnosed between 2013 and 2016.

Strengths of this study include the fact that it is one of the largest studies of the behavior of AIH in this group of patients. (5) Other strengths include follow-up in times which allowed study of the differences in AIH behavior by age group; the percentage of patients (82%) with diagnoses confirmed with liver biopsy; the detailed descriptions of clinical presentation forms, and the evaluations of responses to treatment since these issues were not evaluated in some of the studies on AIH in older adults. (5)

In conclusion, AIH affects adults of all ages, but it is common in those over 65 years of age who have a higher frequency of cirrhosis at the time of diagnosis. By including AIH in the differential diagnosis of liver disease in this group of patients, timely diagnoses and treatment to which patients respond better with less adverse effects can be achieved.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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A randomized controlled clinical trial of the efficacy and safety of colonoscopy preparation using a single four liter dose of polyethylene glycol (PEG) vs. two 2 liter doses of PEG vs. two low volume (1L + 1L) doses of PEG

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Abstract

Introduction: Colonoscopy is the gold standard for evaluation of the colonic mucosa. Colon cleansing in preparation for colonoscopy depends on finding of polyps which can be adenomatous with malignant potential and the possibility of degenerating into colon cancer. **Objective:** This study's objective was to compare the efficacy and safety of three types of preparations for colon cleansing: a single four liter dose of polyethylene glycol (PEG) vs. two 2 liter doses of PEG vs. two low volume (1L + 1L) doses of PEG. **Methods:** This is a randomized controlled clinical trial of patients who underwent elective colonoscopy at a University clinic. It was blinded for the doctor who evaluated colon cleansing. Seventy four patients 74 patients were randomized into each group. The main parameter of effectiveness was integral preparation of adequate quality measured on the Boston scale. Secondary parameters were the percentage of adverse events, tolerability and detection rate of polyps. **Results:** Complete preparation of the entire colon was achieved significantly more often with 4 liters divided into two 2 liter doses followed by the other divided alternative (1 L + 1 L). It was achieved least frequently with in the single dose: 79.7%, 75.7% and 63.5%, respectively, p = 0.019. Differences were also found in the detection of polyps (13.5%, 24.3% and 9.5%, respectively, p = 0.037).) There were no differences in presentation of at least one adverse event (p = 0.254) or in tolerability (p = 0.640). **Conclusions:** The two divided dose preparations had higher colon cleansing and polyp detection efficacies than did the single 4L dose while there were no differences in occurrence of adverse events and tolerability. The divided PEG 2L dose could be a very good option for elective colonoscopy preparation.

Keywords

Efficacy, safety, preparation, colon, polyethylene glycol, low volume.

INTRODUCTION

Colonoscopy, the gold standard for evaluating the mucosa of the colon, (1, 2) is especially important for finding polyps which decreases the incidence and mortality from colon cancer since adenomatous polyps are potentially malignant. (3, 4). Colon cancer is the second leading cancer cause of death in women and the third in men. (5)

Effective preparation for colonoscopy is important because it allows a gastroenterologist to efficiently detect more polyps and other pathologies of the colon. (2, 6) The degree of cleanliness of the colon determines the success of colonoscopy. (7) All colonoscopy examinations should state the quality of the colon preparation. The quality criterion should be to achieve good or very good preparation as measured by the Boston Bowel Preparation Scale (BBPS) in more than 95% of the explorations. (8-14)

Intestinal preparations are evaluated on the bases of three criteria: efficacy, safety and tolerability. The efficacy of different bowel preparation regimens has been assessed and quantified in several studies, systematic reviews and meta-analyzes. Differences of regimens, dosages, dietary restrictions, patient

characteristics, adjuvant agents and assessment methods among the various the studies have led controversy regarding their results. In 2014, the guidelines of the Multi-Society Task Force on Colorectal Cancer (MSTF) in the United States stated that a divided 4 liter dose of PEG with electrolytes provides high quality preparation. The guidelines also indicate that low-volume two liter formulations of PEG achieve intestinal cleansing in healthy patients without constipation and that the results are not inferior to the 4 L formulation. (10) This was supported by a recent metaanalysis of 47 randomized controlled clinical trials with 13,487 patients. It compared a single dose of PEG taken the day before colonoscopy with a divided dose of PEG (Odds ratio [OR] : 2.51; 95% confidence interval [CI]: 1.86-3.39) (15). Tolerability was better with 2 L PEG than with 4 L PEG (OR: 2.23; 95% CI 1.67-2.98). (2, 10, 15, 16) The metaanalysis concluded that more uniform definitions should be developed through studies with parameters such as adverse effects, polyps, detection of adenomas and return to daily activities. (15)

In Colombia, there are only a few studies of colon preparation for colonoscopy. A randomized, double-blind, cost-effectiveness study compared PEG and mannitol in a fourth-level hospital in Bogotá and concluded that both intestinal preparations for diagnostic colonoscopy provide similar colonic cleansing results. They are both safe, reliable and well-tolerated treatments, but Mannitol costs significantly less. (17) Efficacy was not compared.

At the Clínica Universitaria Colombia, PEG is the drug of choice for the gastroenterology service because it has good cleaning efficacy and is very safe for patients with fecal occult blood, digestive bleeding, chronic diarrhea, abdominal pain, and irritable bowel symptoms as well as being sage for colon cancer screening. (18, 19)

Because of the need to optimize quality of preparation, a randomized blinded clinical trial was designed to evaluate the efficacy and safety of colon cleansing with three different PEG preparations including the low volume 2 L divided PEG dose (Two one liter doses each with two envelopes of PEG 3350).

MATERIALS AND METHODS

Study Design

This is a randomized, blind, parallel, controlled clinical trial that evaluates the efficacy and safety of three preparations: 4 L PEG in a single dose, 4 L PEG divided (2 L + 2 L) and divided 2 L PEG (1 L + 1 L). Participants were equally allocated among the 3 groups (74:74:74). The doctor who evaluated colon cleansing using the BBPS did not know which preparation had been used.

Patients

Patients who were 18 to 75 years whose attending physician prescribed colonoscopy due to occult fecal blood, digestive bleeding, diarrhea, abdominal pain, and/or irritable bowel symptoms or for screening and who signed an informed consent form were included. Patients were excluded because of pregnancy, lactation, nausea, chronic vomiting, intestinal obstruction, neurological hypomotility syndrome, severe constipation (less than one deposition per week), colon resection> 50%, known allergy at PEG, major psychiatric disease, history of gastroparesis diagnosed by scintigraphy, and chronic renal failure under treatment by hemodialysis. Patients were selected from the gastroenterology department of the Clínica Universitaria Colombia, a fourth level hospital.

Result Variables

Primary Parameters of the Study

The primary parameters of this study were total scores on the BBPS by segments and integrally (the sum of the three segments) were used. Scores of six or higher were defined as adequate preparation while those under six were defined as inadequate preparation.

Secondary Study Parameters

Secondary study parameters were the percentage of adverse events, the rate of detection of adenomas (polyps) and the percentage of tolerability for the preparation of colon cleansing reported by the patient.

Sample Size

Sample size estimation for evaluation of differences among the three types of preparations was determined at a difference between the minimum preparation or equal preparations of 20% with a reliability of 95% and a power of 90%. The minimum size in the three groups was calculated at 74 (74:74:74) and with a loss adjustment of 10% (82:82:82).

Randomization

The biostatistical epidemiological method of permuted block randomization of patients was used. One was added to an evenly distributed random number between 0 and 1 that had been multiplied by six. Then it was rounded off to the lowest whole number. The possible permutations of the 3 study groups (1. ABC, 2. ACB, 3. BAC, 4. BCA, 5. CAB, 6. CBA) were taken into account. Then, a sequence of 74 random numbers between 1 and 6 were generated in Excel 2013 to obtain 74 random triples.

Three strategies were used to identify patients: 1) outpatients for whom a gastroenterologist indicated a need for colonoscopy; 2) telephone calls to patients scheduled for colonoscopy; and 3) email to patients scheduled for colonoscopy with subsequent telephone explanation. Patients who entered the gastroenterology service consecutively and met the selection criteria were randomly assigned the permutations chosen. Once the patient met the selection criteria including signed informed consent, the investigator gave her or him a sealed and numbered envelope with the previously randomized preparation (which the doctor who assessed the degree of colon cleansing did not know). Subsequently, s/he was given the data collection form which had been evaluated and approved by the Ethics and Research Committee. Forms were filled out and delivered by the patient on the day colonoscopy was performed.

Interventions

All preparations evaluated used either Nulytely® or Klean-Prep® PEG 3350.

Group 1: 4 L PEG divided (2 L + 2 L)

Patients were instructed to dissolve one envelope of PEG in 1 L of water and another envelope of PEG in another liter of water and take them at 8:00 pm the night before the examination. Then the instructions called for patients to repeat this procedure at 3:00 am if colonoscopy was scheduled in the morning. If the colonoscopy was scheduled in the afternoon, the patients were instructed to repeat the procedure at or after 8:00 am.

Group 2: 2 L PEG divided (low volume) (1 L + 1 L)

Patients were instructed to dissolve 2 envelopes of PEG in 1 L of water and take them at 8:00 pm the night before the examination. at 8:00 pm the night before the examination. Then the instructions called for patients to repeat this procedure at 3:00 am if colonoscopy was scheduled in the morning. If the colonoscopy was scheduled in the afternoon, the patients were instructed to repeat the procedure at 10:00 am.

Group 3: 4 L PEG in a single dose

Patients were instructed to individually dissolve 4 envelopes of PEG in 4 L of water. In other words, each envelope of PEG was to be dissolved in one L of water separately from the other three. Then the instructions called for patients to drink all four liters of water with PEG at 8:00 pm the night before the examination, if it had been scheduled for the morning. If the colonoscopy was scheduled in the afternoon, the patients were instructed to drink all four liters of water at 6:00 am on the day of the procedure.

As recommended by the guidelines of the American Society of Anesthesiologists (ASA), patients were asked not to consume any food orally for at least 4 hours prior to the procedure to avoid the risk of aspiration associated with sedation. (2)

Once the colonoscopy had been performed, the doctor who performed the procedure evaluated the cleanliness of the colon according to the BBPS. Scores from 0 to 3 were assigned with 0 indicating inadequate, 1 indicating bad, 2 indicating good and 3 indicating excellent. Cohen's kappa coefficient, a measure of intra-observer reliability, was 0.77. (3, 12, 13).

Data Collection Instrument

The data collection form included information on sex, age, comorbidities, abdominal surgery, type of preparation, evaluation of colon cleansing in three segments according to the BBPS, type of doctor who performed the colonoscopy (gastroenterology fellow or, gastroenterologist). It also included a subjective questionnaire about adverse events including abdominal distension, abdominal pain, vomiting, sleep disturbance and work or school absenteeism, a subjective rating of preparation tolerability of good, tolerable, bad or very bad, and questions about constipation. These questions asked about frequency of bowel movements (defining constipation as a bowel movement once every three or more days), hard feces, excessive effort, and need for digital manipulation to facilitate evacuation. Finally, the form included body mass index (BMI) and whether or not polyps were found during colonoscopy

Ethical Considerations

The clinical trial protocol was approved by the Ethics and Research Committee of the Fundación Universitaria Sanitas and the Organización Sanitas Internacional (CEIFUS 2748-16 of February 19, 2016). Written informed consent was obtained from all patients who participated in the study.

Statistical Analysis

For qualitative variables, simple frequencies and percentages were used to describe clinical and demographic characteristics. For quantitative variables, measures of central tendency (averages and medians) and measures of dispersion (standard deviation and range) were used. Normality of the distributions of numerical variables was evaluated with Kolmogórov-Smirnov tests and the Shapiro-Wilk test. Homogeneity of variances was assessed with Levene's test. Kruskal-Wallis non-parametric analysis of variance

(ANOVA) and multiple KW comparisons were also used. Pearson's χ^2 test was used to measure differences in proportions of qualitative variables among the three preparations, and exact likelihood tests were used to measure expected values less than five. The information was systematized in an Excel 2016 database and debugged and processed with SPSS version 23 (IBM) and Stata 14.0.

RESULTS

A total of 279 patients were evaluated. The effective sample size was 222 patients randomized into three groups (Figure 1).

Demographic and Clinical Characteristics

In the total study population, 60.8% of the study participants were women, and the average age of participants was 49.9 ± 13.1 years. Table 1 shows that there are no significant differences among the groups in terms of demographic and clinical characteristics of the patients included in the study.

Efficacy

Preparation Quality

Cleaning quality was significantly better in the transverse and left colon with the two divided dose preparation schemes than in the single dose scheme. No statistically significant differences were found between the divided dose alternatives. In the right colon, the cleaning quality was better in the 2 L + 2 L divided dose group than in the other two schemes.

Statistically significant differences were found among the three schemes in the overall BBPS (sum of three segments). The highest score was in group 2 L + 2 L and the biggest difference was between that group and the 4 L group. There were no statistically significant differences between the two divided dose groups (2 L + 2 L vs. 1 L + 1 L).

The percentage of excellent or good results for the overall BBPS (≥6) was significantly higher in the 2 L + 2 L alternative, followed by the other divided alternative (1 L + 1 L), and lowest in the single dose (4 L) alternative (Table 2). Statistically significant differences were found in the polyp detection rate. Alternative 1 L + 1 L had the highest detection rate (Table 2).

Safety

At least one adverse event was reported in 113 patients (50.9%). Descriptions of the various adverse events and their frequencies are presented in Table 3. School or work absenteeism was reported for 97 patients (43.7%), and abdominal distention and pain were the most frequently reported events. No statistically significant differences were observed in the study preparation schemes and no differences were found per individual event (when at least one adverse event or an average of adverse events was reported) (Table 3).

The overall tolerability scores of the scale subjectively measured in the data collection questionnaire as good,

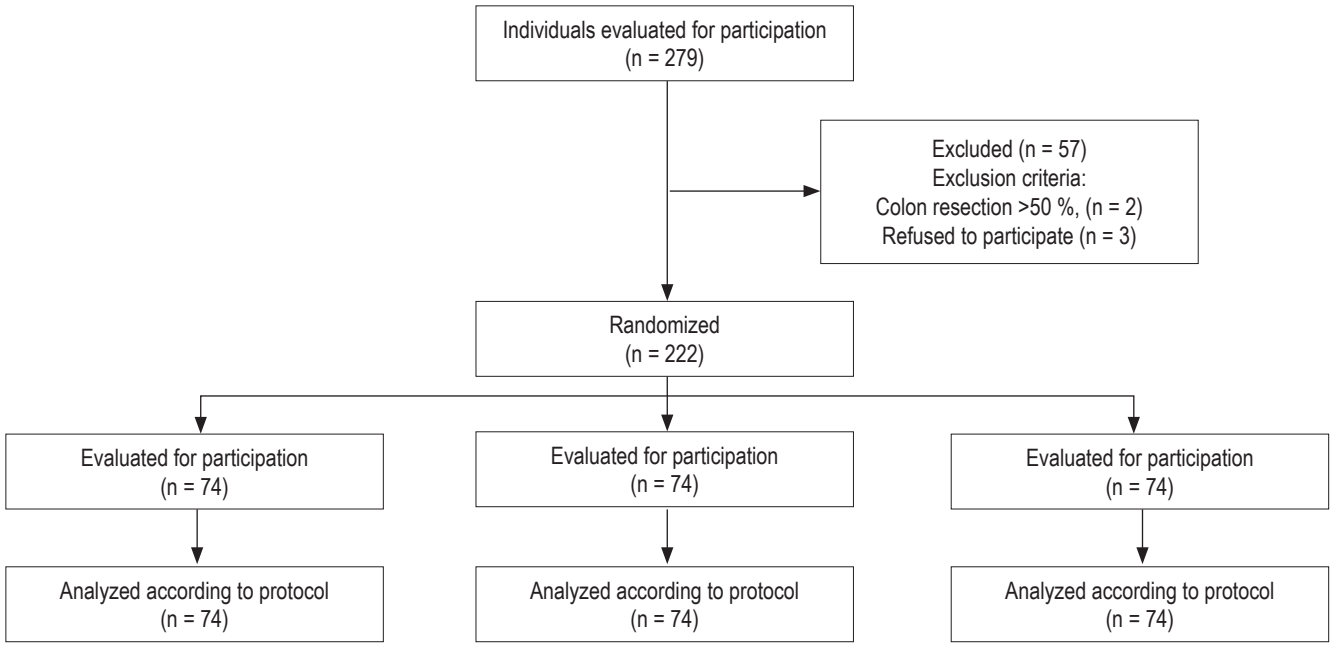

Figure 1. Study Flow Chart

Table 1. Demographic and clinical characteristics among the three preparation scheme groups

	4 L Preparation divided (2 L + 2 L))	Low volume divided preparation (1 L + 1 L)	4 L undivided preparation	*p*
Women, n (%)	49 (66.2)	49 (66.2)	45 (60.8)	0.730
Age in years, Average ± SD	49.4 ± 13.9	52.6 ± 12.2	47.6 ± 12.9	0.060
Overweight, BMI> 25 kg/m^2	34 (45.9)	35 (47.3)	29 (39.2)	0.568
Comorbidities, n (%)	35 (47.3)	28 (37.8)	31 (41.9)	0.505
Abdominal surgery, n (%)	36 (48.6)	36 (48.6)	35 (47.3)	0.982
Examination scheduled in the morning, n (%)	22 (29.7)	21 (28.4)	22 (29.7)	0.979

SD: standard deviation; BMI: body mass index.

Table 2. Measurement of quality of colon cleansing preparation according to preparation scheme

	4 L divided Preparation (2 L + 2 L)	Low volume divided preparation (1 L + 1 L)	4 L undivided preparation	*p*
Right colon				
Excellent	**55 (74.3)**	**44 (59.5)**	**45 (60.8)**	0.050
Good	**14 (18.9)**	**25 (33.8)**	**17 (23.0)**	
Bad	5 (6.8)	5 (6.8)	9 (12.2)	
Inadequate	0	0	3 (4.1)	
Transverse colon				
Excellent	**61 (82.4)**	**58 (78.4)**	**46 (62.2)**	0.019
Good	**12 (16.2)**	**11 (14.9)**	**21 (28.4)**	
Bad	1 (1.4)	5 (6.8)	4 (5.4)	
Inadequate	0	0	3 (4.1)	
Left colon				
Excellent	**64 (86.5)**	**57 (77.0)**	**50 (67.6)**	0.019
Good	**9 (12.2)**	**10 (13.5)**	**16 (21.6)**	
Bad	1 (1.4)	7 (9.5)	5 (6.8)	
Inadequate	0	0	3 (4.1)	
Overall BBPS score, Average ± SD	8.3 ± 1.2 (9)	7.9 ± 1.7 (9)	7.4 ± 2.3 (9)	0.036
Excellent preparation (BBPS ≥8), n (%)	59 (79.7)	56 (75.7)	47 (63.5)	0.069
Excellent or good preparation (BBPS ≥6), n (%)	72 (97.3)	67 (90.5)	62 (83.8)	0.019
Rate of detection of polyps (adenomas), n (%)	10 (13.5)	18 (24.3)	7 (9.5)	0.037

BBPS: Boston Bowel Preparation Scale; SD: standard deviation.

Table 3. Reported adverse effects and patient tolerability of colon preparation

	4 L divided preparation (2 L + 2 L)	Low volume divided preparation (1 L + 1 L)	4 L undivided preparation	*p*
Abdominal pain, n (%)	18 (24.3)	11 (14.9)	16 (21.6)	0.337
Abdominal distension, n (%)	25 (33.8)	17 (23.0)	17 (23.0)	0.228
Vomiting, n (%)	10 (13.5)	6 (8.1)	10 (13.5)	0.498
Sleep disturbance, n (%)	13 (17.6)	18 (24.3)	10 (13.5)	0.231
At least one adverse event	43 (58.1)	37 (50.0)	33 (44.6)	0.254
Adverse event per patient, mean ± SD	0.89 ± 0.93 (1)	0.70 ± 0.87 (0.5)	0.72 ± 0.96 (0)	0.279
Absenteeism, n (%)	33 (44.6)	35 (47.3)	29 (39.2)	0.599
Patient toleration, n (%)	67 (90.5)	68 (91.9)	70 (94.6)	0.640

SD: standard deviation

tolerable, bad or very bad were high, and there were no significant differences among the three schemes.

DISCUSSION

This study was a randomized controlled clinical trial in which the BBPS was used for assessment. The overall sample included 222 patients and had a power of 90%, 95% reliability, and high quality information. Noninferiority of divided dose regimens with PEG for elective colonoscopy was evidenced. Four liter (2 L + 2 L) and low volume (1 L + 1 L) have divided doses high efficacy and safety profiles and have greater efficacy than do single doses. (15) For the transverse and left colon, the scores of the BBPS are better for split-dose regimens than for the single dose 4 L regimen. This is an important result, because divided doses could become the recommended system for colon cleansing before elective colonoscopy, as shown by the studies by Martel et al. (15) (OR 2.51; 95% CI 1.86- 3.39), Téllez-Ávila et al. (20) (p = 0.045) and Kilgore et al. (19) (OR 3.70; 95% CI 2.79-4.91) and as already shown in literature. (18, 21-24)

The efficacy of the low volume regimen (1 L + 1 L) is comparable with that of the normal divided volume (2 L + 2 L) for the preparation of the colon in elective colonoscopy. It is important to note that our Spanish and English literature search found no studies on low volume divided PEG regimens, which makes this study novel.

No statistically significant differences were found in colon cleansing between the two divided dose regimens for any of colon segments, nor were statistically significant differences found for frequency of adverse effects among the three regimens that were compared. This result would indicate that low volume alternatives can be recommended equally. To our knowledge, this is the first study that evaluates a divided low volume dose of 2 L. It shows no inferiority with respect to the alternatives evaluated. In the literature, only single low volume doses have been evaluated. They were found to be more effective and to have less adverse effects in the article published by Téllez-Ávila et al. in Mexico. They concluded that divided-dose and low-volume preparations were better than a single 4 L dose the day before the examination. (20)

Our study found significant differences in the rates of detecting adenomas (p = 0.037) between the 2 L + 2 L and the 4 L single dose schemes. The detection of adenomas was higher in divided doses, especially in the 1 L + 1 L scheme. This finding should be subjected to additional analyses because the differences between the divided preparations cannot be attributable to the differences in the quality of the preparation as they were similar in the two divided dose groups.

Limitations

This analysis has some limitations. First, it was not possible to blind the patients to the alternative that they used even though the endoscopist was blinded at the time of the evaluation of the scale. Second, the patients took the preparation at home without direct control by researchers. Nevertheless, this mitigated by strict control and telephone and email follow-ups to remind, advise and guarantee compliance with instructions. Third, tolerability was assessed with a scale that had not been validated, so its results should be interpreted with caution. However, the main outcome, colon cleansing, was assessed with a validated instrument, the BBPS.

CONCLUSIONS

The two divided dose schemes, 4 L (2 L + 2 L) and low volume 2 L (1 L + 1 L), were most effective for colon cleansing according to the overall BBPS scores. No differences in safety were found between divided dose and single dose preparations. Both divided dose preparations were better than the single 4L dose given the day before the colonoscopy was performed. Polyps detection was greatest with the divided 2 L + 2 L dose.

Conflicts of Interest

None declared for this study.

Funding Source

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Diagnosis and treatment of patients with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) at a university hospital in Colombia

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Abstract

Introduction: Hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu syndrome) is a hereditary vascular disease characterized by recurrent epistaxis, gastrointestinal bleeding and chronic anemia. Many cases have arteriovenous malformations of solid organs. Diagnosis is based on clinical data, endoscopy and imaging. Early detection and treatment of complications with a multidisciplinary approach impacts the disease's morbidity and mortality. **Objectives:** The objective of this study was to describe the demographic, clinical and outcome characteristics of patients diagnosed with HHT at a university hospital. **Methods:** This is a case series of patients evaluated between 2012 and 2017. **Results:** Records of 18 cases were obtained. The patients were from Colombia and other Caribbean countries. All diagnoses were established using the Curaçao criteria. Eleven patients 11 (61.1%) were men, and the median patient age was 56 years (IQR 52-64). The median number of hospital admissions was 6 (33.3%) (IQR 2.5-20.5), and all admissions were related to bleeding. Sixty-one percent of patients required transfusion of blood products, and the compromises of solid organs were found in the same number of patients by imaging studies. **Conclusions:** The clinical expression of THH varies, but in our study gastrointestinal manifestations were the most frequent causes of hospital admission. They frequently required transfusion of blood products and patients required multiple studies to identify the extent of the disease, and solid organ compromise. Treatment was based on endoscopic and medical management, especially administration of bevacizumab and octreotide.

Keywords

Hereditary hemorrhagic telangiectasia, hemorrhage, epistaxis, melena.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu disease (OWRD) is an autosomal dominant inherited vascular disease with various clinical manifestations. Patients usually present epistaxis, gastrointestinal bleeding and iron deficiency anemia due to mucocutaneous telangiectasias. Patients with HHT are also said to be at risk of developing arteriovenous malformations which can cause serious organ damage especially in cerebral, pulmonary and hepatic circulation. (1) Initial detection of HHT is based on clinical data, and the Curacao criteria are often used (Table 1). These consist of recurrent epistaxis, telangiectasias, visceral vascular malformations and a first-degree relative with HHT (the diagnosis is established with three or more of these criteria). (2, 3) Treatment of this entity consists of managing symptoms and complications. (3)

The estimated prevalence of HHT is 1.5 to 2.0 people per 10,000. (4, 5) Some authors think that variable penetrance (complete and incomplete) could have impact recognition and notification of the disease since not all patients present symptoms at an early age. (3, 4) This entity has a higher prevalence in certain populations including the Afro-Caribbean population of Curaçao and Bonaire. (5) To date, there have been very few case series published in Latin America, but there are reports of isolated cases in which variable clinical manifestations and involvement of solid organs due to arteriovenous malformations have been described. (6-8)

Table 1. Curacao diagnostic criteria for hereditary hemorrhagic telangiectasia

Criteria	Epistaxis or spontaneous and recurrent nosebleed.
	Telangiectasias at multiple characteristic sites (lips, oral cavity, fingers and nose).
	Visceral lesions, telangiectasias in the gastrointestinal tract (with or without bleeding) or pulmonary, hepatic, cerebral and spinal arteriovenous malformations.
	Family history: first-degree relative with a diagnosis of HHT.
Diagnosis	Definitive if 3 or more criteria are met.
	Possible or presumed if 2 criteria are met.
	Unlikely if less than 2 criteria are met.

The objective of this work is to describe demographic and clinical characteristics as well as outcomes of patients diagnosed with HHT at a university hospital.

MATERIALS AND METHODS

This is a case series study of patients older than 18 years of age with diagnoses of HHT established in the hospital from January 2012 to July 2017. The protocol was approved by the ethics and research committee of the Hospital Pablo Tobón Uribe in Medellín, Colombia. No written authorization was required since no names, personal identity data, or photos which would allow recognition of any individuals are included in the published data. According to National Resolution 8430 of 1993, this is a minimum risk study that does not jeopardize the integrity or identity of any patients.

The review of the medical records and procedures performed on the individuals under study was carried out between January 2012 and July 2017.

Data Collection and Analysis

Variables were loaded into a database by the researchers, and descriptive statistics such as measures of central tendency including means, medians and ranges were used for analysis.

RESULTS

Records of 18 cases were obtained (Tables 2 and 3). There were 11 men (61.1%) and 9 women (29.9%) with a median age of 56 years (interquartile range [IQR]: 52-64). Six were from Antioquia (33.3%), four from Chocó (22.2%), two from Caldas (11.2%), one from Quindío (5.5%), one from

Table 2. Demographic and clinical characteristics of patients with HHT.

Case	Age/sex	Place of Origin	Family history	Symptoms at consultation	Minimum platelet count	Minimum hemoglobin level	Solid organ compromise
1	58/M	Riosucio, Caldas	Yes	Asthenia, adynamia, fatigue, dyspnea, epistaxis, melena, hematochezia	88,000	3.7 g/dL	Yes (liver)
2	62/F	Cali	ND	Hematochezia, asthenia, adynamia, dyspnea	144,000	6.3 g/dL	Yes (liver, lung, pancreas)
3	52/M	Curaçao	Yes	Epistaxis, gastrointestinal bleeding	125,000	5.4 g/dL	Yes (liver)
4	41/F	Medellín, Antioquia	No	AUH, spontaneous ecchymosis	359,000	12.6 g/dL	None
5	77/M	Andes, Antioquia	No	Melena	166,000	5.1 g/dL	None
6	54/F	Riosucio, Caldas	Yes	Epistaxis, melena, hematochezia	208,000	7.4 g/dL	None
7	63/M	Curazao	Yes	Hemoptysis, melena, epistaxis	231,000	5.3 g/dL	Yes (lung)
8	59/F	Lloró, Chocó	Yes	Epistaxis, melena, hematochezia	ND	8.7 g/dL	None
9	56/F	Lloró, Chocó	No	Asthenia, adynamia, epistaxis	131,700	7.6 g/dL	Yes (liver, lung, brain)
10	78/M	Bonaire	ND	Epistaxis, asthenia, adynamia, fatigue, paleness	224,000	7.4 g/dL	Yes (lung)
11	67/M	La Unión, Antioquia	No	Melena	110,000	3.6 g/dL	Yes (lung)
12	58/M	Bonaire	No	Melena	416,000	8.9 g/dL	None
13	52/M	Bello, Antioquia	Yes	Epistaxis	241,000	16 g/dL	Yes (liver)
14	56/F	Quibdó, Chocó	Yes	Melena, epistaxis	134,000	4.9 g/dL	None
15	27/M	Lloró, Chocó	Yes	Epistaxis	ND	ND	Yes (lung, brain)
16	72/M	Riosucio, Caldas	Yes	Asthenia, adynamia	262,000	7.1 g/dL	None
17	48/F	Medellín, Antioquia	No	Epistaxis	264,000	ND	Yes, (lung, brain)
18	55/M	Medellín, Antioquia	Yes	Epistaxis, abdominal pain	234,000	6 g/dL	Yes (liver)

F: female, AUH: abnormal uterine hemorrhaging, M: male, ND: no data.

Table 3. Clinical data on treatment of cases with HHT

Cases	Hospital admissions	Peripheral stigmas: mucocutaneous	Digestive tract telangiectasias	Medical therapy	Endoscopic procedures	Transfusion of blood products (units)
1	74	Nose, hands	Esophagus, stomach, duodenum, jejunum, ileus, colon	Endoscopy, bevacizumab	UDE 8, enteroscopy 1, EVC 1	Yes (179 U)
2	40	ND	Esophagus, stomach, duodenum	Endoscopy, bevacizumab	UDE 10, EVC	Yes (2 U)
3	15	Tongue	Duodenum, jejunum	Endoscopy, bevacizumab, thalidomide, tamoxifen	UDE 2, EVC 1, enteroscopy 1	No
4	11	Hands and trunk	ND	None	ND	No
5	9	Face	Esophagus, stomach, duodenum, jejunum	Endoscopy	UDE 6, colonoscopy 1, EVC 1, enteroscopy 1	Yes (35 U)
6	37	Tongue and fingers	Stomach, colon	Endoscopy	UDE 19, colonoscopy 2, EVC 1	Yes (1 U)
7	46	Tongue, lips Hands	Esophagus, stomach, duodenum, jejunum	Endoscopy, bevacizumab	UDE 5, colonoscopy 1, enteroscopy 1, EVC 1	Yes (6 U)
8	7	Tongue, palate	Hypopharynx, stomach, duodenum, jejunum	Endoscopy	UDE 2, colonoscopy 1, EVC 1	ND
9	8	ND	Stomach, duodenum	Endoscopy	UDE 1, colonoscopy 1, EVC 1	Yes (2 U)
10	5	ND	Stomach, duodenum	Endoscopy	UDE 2, EVC 1, enteroscopy 1	Yes (1 U)
11	3	Lips, palate, nose	Stomach	Endoscopy	UDE 19, colonoscopy 2, EVC 1	Yes (13 U)
12	4	ND	Stomach, duodenum, jejunum, ileus	Endoscopy, octreotide	UDE 3, EVC 1, enteroscopy 1	No
13	3	Tongue	None	None	UDE 1	No
14	3	Tongue, lips	Stomach, duodenum, jejunum	Endoscopy	UDE 8, colonoscopy 1, EVC 1, enteroscopy 1	Yes (32 U)
15	1	ND	ND	Bevacizumab	ND	ND
16	1	Nose, tongue, lips	Stomach, duodenum, jejunum	Endoscopy, octreotide	UDE 1, colonoscopy 1, enteroscopy 1, EVC 1	Yes (2 U)
17	1	ND	Stomach	None	UDE 1	ND
18	1	Tongue, lips	Stomach, duodenum, jejunum	Endoscopy	UDE 1	Yes (2 U)

UDE: upper digestive endoscopy; U: units; EVC: endoscopic videocapsule.

Valle (5.5%), three from Bonaire (16.7%) and one from Curacao (5.5%).

First-degree family histories of HHT reported by 55.55%, six cases (33.33%) were spontaneous. There were no background data on the medical history of only two people (11.11%). The two patients from Riosucio,Caldas; one patient from Curaçao and one patient from Bonaire had first-degree family histories, and three of the four patients (75%) from Chocó had family histories of HHT.

Symptoms at admission were epistaxis (66.7%), melena (50%), hematochezia (22.22%), asthenia-adynamia (27.8%), fatigue (11.11%), dyspnea (11.11%). One patient had hemoptysis, and another patient had ecchymosis and abnormal uterine bleeding.

Endoscopy was performed and registered in the medical histories of 16 patients (88.8%), but there were no records of endoscopy in the clinical histories of the other two patients. All patients who underwent endoscopic studies had upper digestive endoscopy, endoscopic videocapsules had been used in 13/16 (81.25%), enteroscopy in 50% and colonoscopy in 50%.

Ten of the patients (55.55%) were admitted to the hospital for emergencies related to digestive bleeding manifested by melena or hematochezia. The minimum hemoglobin

levels in this group of patients ranged from 3.6 to 8.9 g/dL. All endoscopic studies including video capsules were performed on these ten patients (Table 3). Seven of them (70%) required enteroscopy for argon plasma coagulation of bleeding lesions or those at risk of bleeding (Figure 1).

Bevacizumab was administered in 27.7% of the cases, octreotide in 11.1%, thalidomide in 5.55% and tamoxifen in 5.55%.

The median hospital stay was six days (IQR: 2.5-20.5). All of these cases were patients hospitalized for digestive bleeding, and 61% of these patients required transfusion of blood products (Table 3). In 61% of these patients, solid organ involvement was identified due to arteriovenous malformations in the liver, lung, brain or pancreas. Four (22.2%) had exclusive liver compromises, three (16.7%) had exclusive lung compromises, and the others had multiorgan compromises: one patient in the liver, lung and pancreas; another patient in the liver, lung and brain; and two other patients in the lung and brain.

Table 2 describes the sex, age, blood test results during hospitalization (minimum platelet count and hemoglobin), and solid organ involvement due to arteriovenous malformation. Table 3 shows clinical manifestations, visible physical findings, distribution of telangiectasias in the digestive tract (Figure 2), and treatments and transfusions received.

DISCUSSION

Most patients in our series had minor bleeding episodes at early ages that were underestimated. Several reviews describe that more than half of these patients have symptoms before 20 years of age and say that the prevalence of epistaxis may be even greater than 90% of cases. (9, 10) The most frequently described symptom was epistaxis. It was followed by melena, hematochezia and general symptoms of blood loss such as asthenia, adynamia, fatigue and even dyspnea. The majority had severe anemia with varied related symptoms and were in need of blood transfusions as

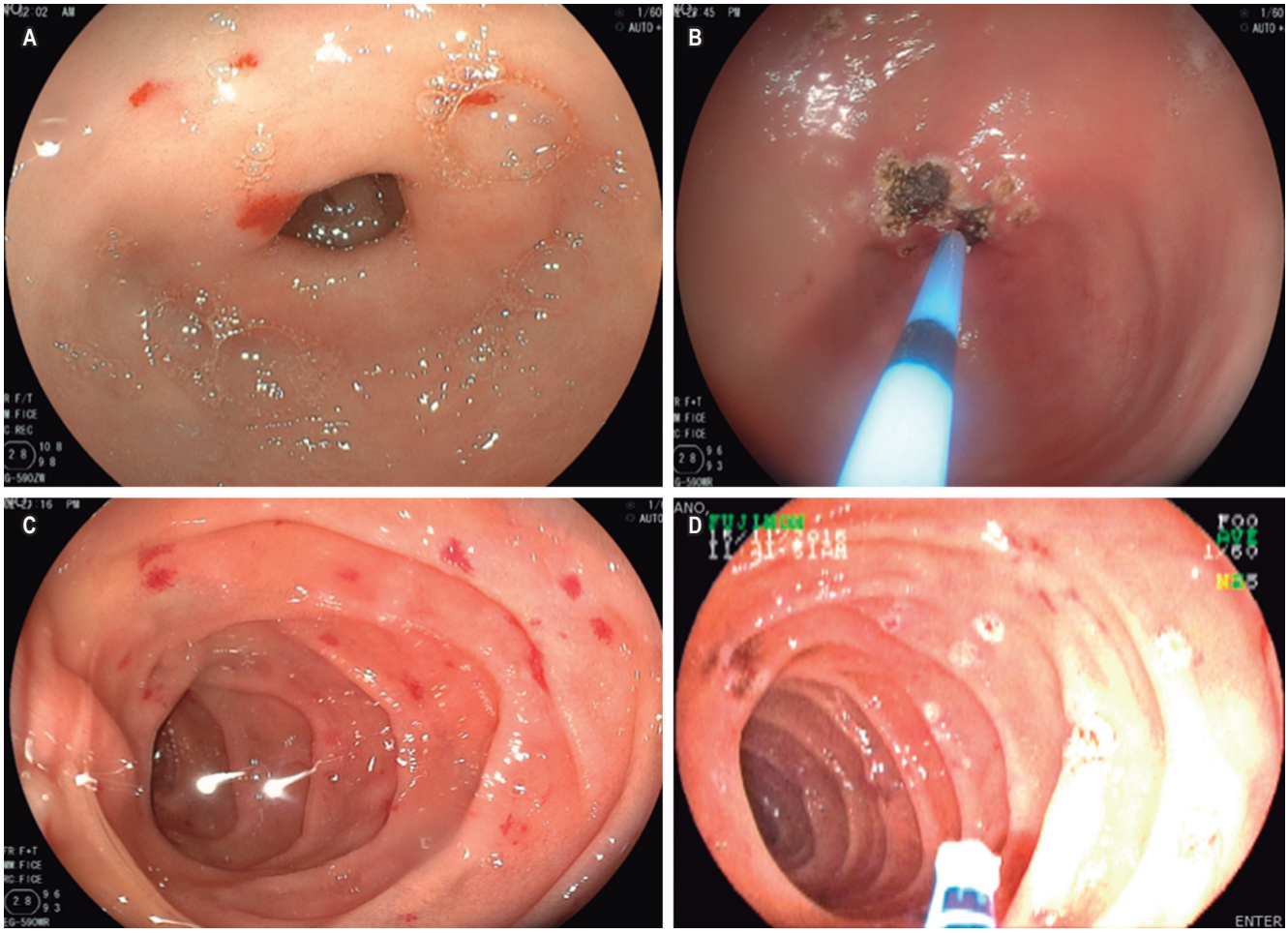

Figure 1. A. Telangiectasias in the antrum. B. Argon plasma therapy on lesions in the antrum. C. Telangiectasias in the small intestine. D. Argon plasma therapy.

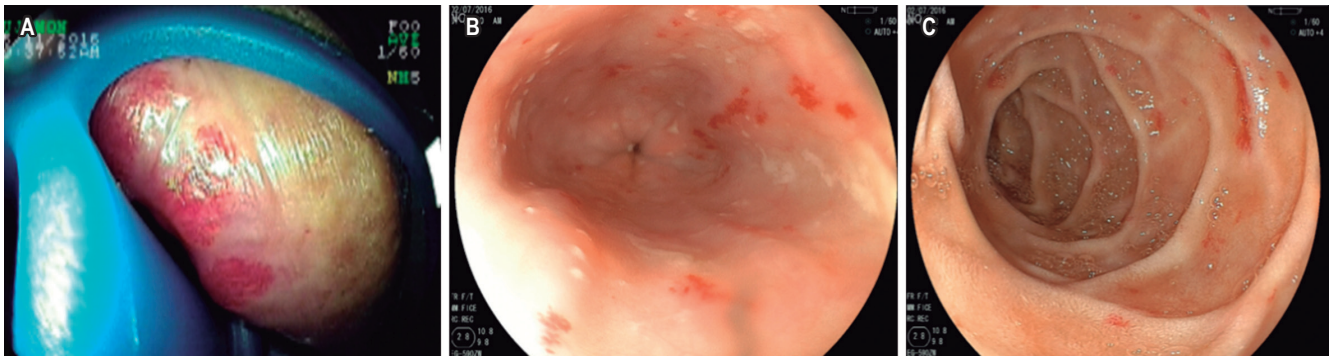

Figure 2. Extensive compromise by HHT. **A.** Lips. **B.** Multiple telangiectasias in the stomach. **C.** Telangiectasias in the duodenum.

described in a recent systematic review. (3) The number of units of red blood cells transfused had a clear relationship with the extent and severity of the disease.

In our series, no patient underwent genetic studies to determine the presence of HHT-related genes. These exams are not widely available in our environment and they are expensive. In addition, there is controversy over variable clinical expression. In a recent study, no significant differences in mortality were found in a period greater than 90 months between HHT Types 1 and 2. (11)

In patients with documented telangiectasias in the digestive tract, the lesions were mostly found in proximal locations. The stomach, duodenum and jejunum were the most common sites. In most cases, EVCs were used as a non-invasive method to assess compromises in the small intestine and define the need for endoscopic therapy. These data are similar to those described in the systematic review by Jackson et al. (3) In cases where bleeding in the small intestine was evidenced, double balloon enteroscopy was used to apply argon plasma therapy, with or without systemic therapy.

Systemic therapy was used in cases with refractory bleeding. Given descriptions in the literature of increased production of vascular endothelial growth factor in patients with this entity, there could also be an imbalance between anti-angiogenic and pro-angiogenic factors. (12, 13) This has allowed the use of drugs such as bevacizumab whose mechanism of action is to inhibit the growth factor of the vascular endothelium. There are multiple case reports of adults such as by Combariza et al. (14) of Hospital Pablo Tobón Uribe in Medellín. Bevacizumab has also been used in small series of cases that highlight good results in terms of effectiveness and safety. (15, 16) However, the costs and profile of adverse events with bevacizumab is not negligible, (17) so an appropriate patient choice must be made in order to opt for this drug. Nevertheless, we believe bevacizumab could be a promising medicine in the scenario of multiorgan involvement and refractory bleeding.

Arteriovenous malformations compromising one or more solid organs was identified in more than 60% of the cases. Most of them had pulmonary or hepatic involvement but a few also had cerebral involvement. The methods described in the literature for detecting these malformations vary. Jackson et al. found that thematic experts recommend studying pulmonary arteriovenous malformations with transthoracic contrast echocardiography and complementing it with high-resolution thoracic computed tomography if there are any abnormal findings. (3) Hepatic vascular malformations are studied in patients with confirmed HHT when they have abnormal liver function tests, cholestasis, portal hypertension or right heart failure. The study of these cases is performed by hepatic ultrasound with Doppler or three-phase helical CT. (18-20) In our series, all cases were studied by means of magnetic resonance imaging (MRI) of the abdomen. Our hospital has good high experience with this exam, and there is less risk of nephrotoxicity than with the use iodinated contrast.

Cerebral arteriovenous alterations were identified in three patients (16.6%) which is very similar to the 10% prevalence found by Fulbright et al. with cerebral MRI. (21) This is the method most often used in asymptomatic patients with possible or confirmed HHT who are 18 years of age or older. (3)

The majority of individuals with HHT who have good access to health services have normal life expectancy in relation to the general population. (3) Distribution of mortality is bimodal with peaks at 50 years and between 60 and 79 years. Acute complications related to arteriovenous malformations are the main cause of death, especially in the context of inadequate health care since these patients play a fundamental role. (3, 22)

We believe that more population studies are required to determine actual local prevalence: Prospective studies in which treatment alternatives aimed at reducing morbidity rates and number and durations of hospital stays are also

needed as are proposals for follow-up of asymptomatic first-degree relatives.

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Structured review of establishing and evaluating clinical relevance of drug interactions in hepatitis C virus treatment (Update 2015 - 2017)

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Abstract

Objective: This study-s objective is to establish and evaluate the clinical relevance of drug interactions during treatment of patients with hepatitis C. **Method:** A PubMed/MedLine search was conducted for articles published in English and Spanish from January 1, 2015 to March 30, 2017 using the terms Mesh: Hepatitis C AND drug interactions OR herb-drug interactions OR food-drug interactions, from studies conducted in humans. The clinical relevance of drug interactions was established and evaluated based on probability of occurrence and severity of interactions. **Results:** Of the 184 four articles identified, 92 were selected by title and abstract for full review. The full texts of two articles could not be accessed. Of the remaining articles, 57 describ ed relevant interactions. Of the 155 pairs of drugs that interact that were identified, 154 (99.4%) were pharmacokinetic, and one (0.6%) was pharmacodynamic. Thirty-four of the 155 pairs (21.9%) were assessed at level 1; 73 (47.1%) were assessed at level 2; 48 (31.0%) were assessed at level 3, none were assessed at level 4. In addition, 29 pairs of interacting drugs had no evidence of clinical relevance. **Conclusions:** More than 99% of clinically relevant drug interactions are pharmacokinetics and are associated with changes in metabolism and transport of drugs. Simeprevir and 3D (Paritaprevir/Ritonavir+ Ombitasvir+Dasabuvir) therapy had the greatest number of interactions.

Keywords

Drug interactions, hepatitis c, antivirals.

INTRODUCTION

Viral hepatitis is considered to be a public health problem worldwide. It has high morbidity and mortality rates, multiple virus serotypes, various transmission routes, and coinfections with human immunodeficiency virus (HIV). In addition, various drugs are used to treat complications and comorbidities, and access to diagnostic methods and effective and safe treatments is limited. (1-3) According to the World Health Organization (WHO), it is estimated that prevalence of hepatitis C virus (HCV) infections in the United States is 1.0%, or 7,000,000. Some authors have estimated that, globally, there are approximately 185 million people who have HCV. (4, 5)

HCV is characterized by two phases of infection. In the first asymptomatic acute phase, 15% to 45% of patients eliminate the virus spontaneously within 6 months and do not progress to the next phase. The other 55% to 85% of patients enter the chronic infection phase which involves the onset of complications such as liver fibrosis, cirrhosis and hepatocellular carcinoma. (3, 4)

In recent years, treatment for HCV has undergone considerable changes. In 2011, the first direct-acting antivirals (DAA) boceprevir and telaprevir (NS3/4A protease inhi-

bitors) appeared. (4) They have increased sustained viral responses (SVR) from 60% to 75% in patients without prior treatment. (6) Since then, new DAAs such as nonstructural protein 5A (NS5A) inhibitors, NS5B nucleoside analogue inhibitors, polymerase inhibitors, and non-nucleoside NS5B polymerase inhibitors have been developed. They attack virus replication by inhibiting different proteins to achieve better SVR rates (> 90% to 95%), increased tolerability of treatment, less associated adverse events and less drug interactions. (3)

Some of the new DAAs as well as other drugs that are widely used in clinical practice converge on metabolism through cytochrome P450 (CYP) isoenzymes and transporters such as glycoprotein-p (Gp-p), organic anionic transporter polypeptides (OATP), and breast cancer resistant protein (BCRP). (7) This makes it necessary to update previously systematized information on severity and probability of occurrence of drug interactions in patients with HCV genotype 1. (8, 9)

METHOD

We searched PubMed/MedLine for articles published in Spanish or English from January 1, 2015 to March 30, 2017 using the following Mesh terms: Hepatitis C AND drug interactions OR herb-drug interactions OR food-drug interactions.

Inclusion Criteria

We considered systematic reviews, metaanalyses, multicenter studies, randomized controlled clinical trials, quasi-experimental studies (non-randomized), observational studies, guidelines, letters and case reports as long as they were human studies in Spanish or English and there was access to the full text. Articles about drug interactions between drugs used to treat HCV and other drugs were considered and, in some cases, references used in those articles were added to increase context and document results.

Exclusion Criteria

We excluded articles about in-vitro and/or animal studies, articles about experimental drugs, and those that did not address drug interactions related to treatment of HCV.

Review Methods

The articles included were independently selected by three researchers. Titles and abstracts of all the articles identified were reviewed to decide upon eligibility. The three authors together analyzed articles selected and decided about inclusion or exclusion of each article by consensus.

Outcome Measures and Assessment of Clinical Relevance of Interactions

Clinical relevance of drug interactions was defined using the severity and probability of occurrence of the interaction. (9) Three categories of severity were considered:

- *Severe:* The interaction may harm or injure the patient. The consequence of a negative clinical outcome of pharmacotherapy might cause patient death, risk to life, hospitalization, permanent or significant disability, congenital anomalies, or malformations at birth. In addition, there may be other effects that, in medical judgment, could compromise the integrity of a patient and require surgical intervention to avoid death, hospitalization or congenital anomalies.
- *Moderate:* The interaction requires monitoring of the patient. The consequence of a negative clinical outcome of pharmacotherapy could modify, change or interruption pharmacotherapy or require the use of additional drugs to treat a problem related to drugs or to prolongation of hospitalization.
- *Mild:* The interaction does not harm the patient. The consequence of a negative result from the drug does not require modification, change or withdrawal of the pharmacotherapy and does not require the use of new drugs to treat a drug-related problem or prolongation of hospitalization.

Three categories of probability of interaction occurrence were established on the basis of the type of study documenting the interaction.

- Defined: interaction documented in metaanalyses, systemic reviews, randomized clinical trials or non-randomized clinical trials.
- Likely: interaction documented in analytical studies or by three or more clinical cases.
- Possible: interaction documented by less than three clinical cases.

From the possible combinations of severity and probability of occurrence, the interactions can be grouped into 4 categories.

- Level 1 (very high risk) results from a combination of serious and defined, or serious and probable. Simultaneous use of drugs is considered to be absolutely contraindicated.
- Level 2 (high risk) results from a combination of serious and possible, moderate and defined, or moderate and

probable. Concomitant use of drugs requires dose adjustment from the dosage schedule and assessment of signs and symptoms of effectiveness and safety of pharmacotherapy, ideally quantitatively.

- Level 3 (medium risk) results from a combination of moderate and possible, mild and defined, or mild and probable. Simultaneous use of drugs requires dosage adjustment or assessment of signs and symptoms of effectiveness and safety of treatment, ideally quantitatively.
- Level 4 (low risk) results from the combination of mild and possible. The interaction is of little clinical relevance.
- Evidence of absence of interaction results from safe combinations of drugs that do not change the magnitude and effect of the drugs involved.

Information Collection Form

A form for collection and tabulation of data about drug-drug interactions related to treatment of HCV was designed on Excel 2016 for Windows®. It had the following structure: pharmacological group of the concomitant drug; interaction class (drug-drug, phytotherapeutic drug, drug-food, drug-disease); pair of interacting drugs; level, severity and probability of occurrence of the interaction; bibliography; interaction mechanism (pharmacokinetics or pharmacodynamics); details of the mechanism of interaction; observations; and recommendations.

RESULTS

The search terms *Hepatitis C AND drug interactions OR herb-drug interactions OR food-drug interactions* identified 184 articles, of which 90 met the inclusion criteria. Of these, 57 reported new HCV treatment drug interactions and met the inclusion criteria (Figure 1). One hundred eighty-four pairs of interacting drugs were identified, of which 155 contributed new interactions or updates to the previous review (Table 1): 34 (21.9%) were level 1, 73 (47.1%) were level 2, and 48 (31.0%) were level 3. Of the new interactions,

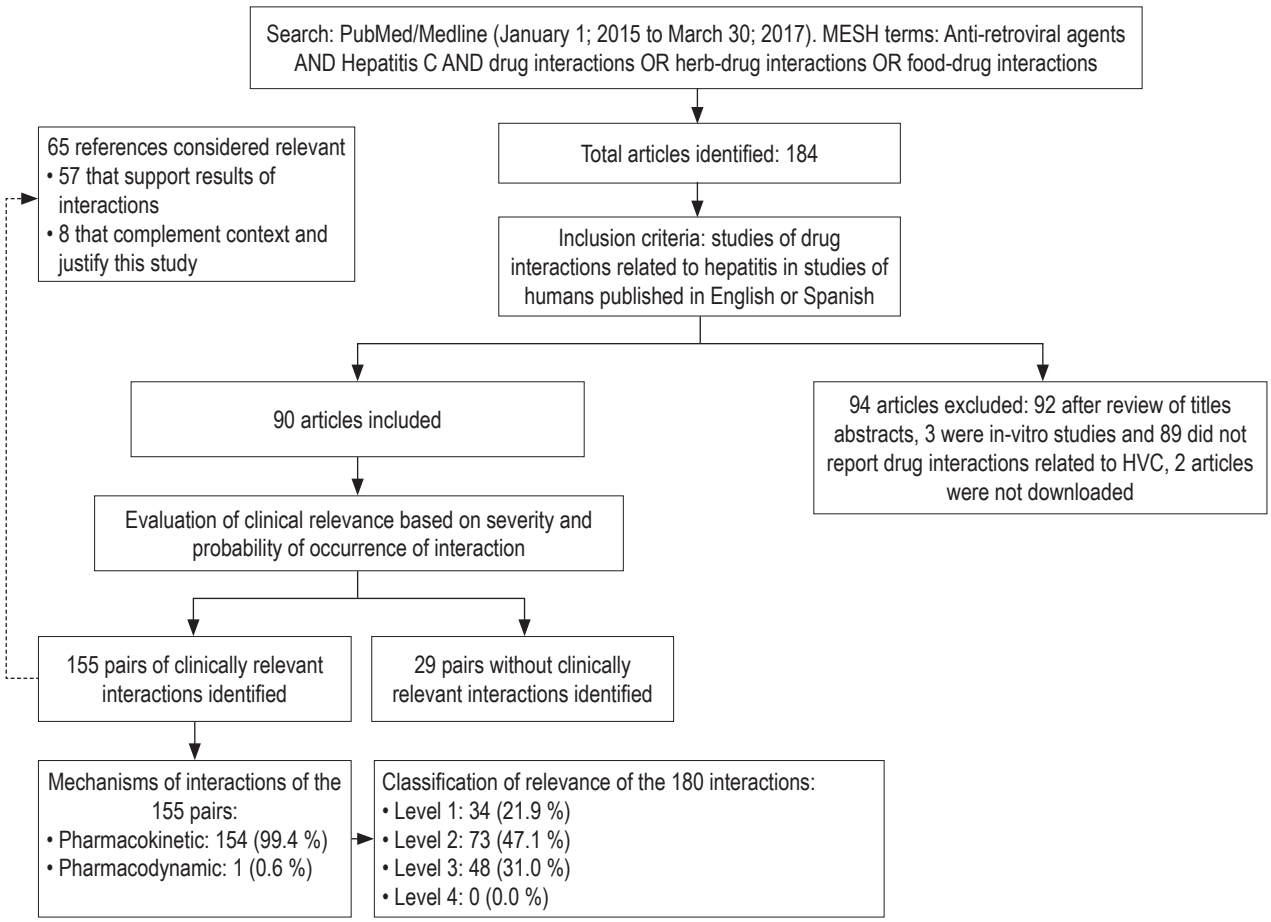

Figure 1. General scheme of structured review of clinical relevance of drug interactions in the treatment of patients infected with HCV.

Table 1. Overall results from 155 pairs of clinically relevant drug interactions

Mechanisms of the 155 pairs of interactions
Pharmacodynamics: 1 (0.6%)
Pharmacokinetics: 154 (99.4%)
Synergism: 1 (0.6%)
Enzymatic inhibition: 70 (45.2%)
Enzymatic induction: 25 (16.1%)
Change in bioavailability: 56 (36.2%)
Excretion inhibition: 3 (1.9%)

Drug	Detail of pharmacokinetic mechanism				Clinical relevance of drug interaction				
	Enzymatic inhibition	Enzymatic induction	Changes in bioavailability	Excretion inhibition	Level 1 n (%)	Level 2 n (%)	Level 3 n (%)	Level 4 n (%)	Total n (%)
ASV	4	1	2	0	2 (1.3)	1 (0.6)	4 (2.6)	0 (0.0)	7 (4.5)
DCV	4	3	1	1	0 (0.0)	5 (3.3)	4 (2.6)	0 (0.0)	9 (5.9)
DNV	1	0	0	0	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
DNV/RTV	1	0	0	0	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
EBR	3	1	0	0	0 (0.0)	4 (2.6)	0 (0.0)	0 (0.0)	4 (2.6)
FDV	2	0	1	0	0 (0.0)	2 (1.3)	1 (0.6)	0 (0.0)	3 (1.9)
GZR	3	1	0	0	3 (1.9)	1 (0.6)	0 (0.0)	0 (0.0)	4 (2.6)
GZR/EBR	0	1	0	0	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
IFN	0	2	0	0	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.3)
LDV	1	1	4	0	0 (0.0)	4 (2.6)	2 (1.3)	0 (0.0)	6 (3.9)
OMB	0	1	0	0	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
PTV/RTV, OMB + DSB	24	6	4	0	10 (6.5)	16 (10.3)	8 (5.2)	0 (0.0)	34 (21.9)
PTV/RTV, OMB	2	1	6	0	1 (0.6)	5 (3.3)	3 (1.9)	0 (0.0)	9 (5.9)
SIM	22	5	4	1	13 (8.4)	10 (6.5)	9 (5.8)	0 (0.0)	32 (20.7)
SOF	1	0	15	1	4 (2.6)	3 (1.9)	10 (6.5)	0 (0.0)	17 (11.0)
SOF/LDV	0	1	12	0	0 (0.0)	8 (5.2)	5 (3.3)	0 (0.0)	13 (8.4)
SOF/RBV	0	0	2	0	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.3)
SOF/DCV/RBV	1	0	0	0	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)
VEL	1	1	5	0	0 (0.0)	7 (4.5)	0 (0.0)	0 (0.0)	7 (4.5)
Total	70	25	56	3	33 (21.3)	73 (47.1)	48 (31.0)	0 (0.0)	154 (99.4)

ASV: asunaprevir; DNV: danoprevir; DSB: dasabuvir; EBR: elbasvir; FDV: faldaprevir; GZR: grazoprevir; IFN: interferon; LDV: ledipasvir; OMB: ombitasvir; PTV: paritaprevir; RTV: ritonavir; RBV: ribavirin; VEL: velpatasvir.

140 (90.3%) were pairs of drug-to-drug interactions, five (3.2%) were phytotherapeutic drugs, eight (5.2%) were medicines with special conditions, and two (1.3%) were medicines with food. Of the 155 pairs, 154 reported interactions of the pharmacokinetic mechanism, especially enzymatic inhibition (70; 45.2%), enzymatic induction (25; 16.1%), changes in bioavailability (56; 36.2%) and excretion inhibition (3; 1.9%).

In one of these three cases of excretion inhibition, it was shown that exposure to daclatasvir (DCV) increases up to two times in patients with severe renal impairment but remains within the range of therapeutic safety and does not require adjustments. (7, 10) Simeprevir (SIM) exposure increases 62% which requires monitoring and dose adjustment. (11-13) Sofosbuvir (SOF) is contraindicated in patients with creatinine clearance over 30 mL/min by increased plasma SOF levels and circulating inactive metabolite GS-331007. (4, 6, 7, 10, 11, 14-20)

Only one case (0.6%), that of DCV and the amiodarone antiarrhythmic, was an interaction using a pharmacodynamic mechanism. It resulted in asymptomatic severe bradycardia. (21)

Table 2 shows levels of clinical relevance. One hundred eight interactions (69.7%) were assessed with a higher

risk of generating problems of effectiveness and safety of DAA drugs. Of these, 53 (34.2%) were due to enzymatic inhibition, 17 (11.0%) were due to enzymatic induction (Table 3) and 34 (21.9%) were due to changes in bioavailability (Table 4). Twenty-nine pairs of drugs were identified with evidence of absence of clinically relevant interactions. Of these, eight were related to ASV, six to LDV, three to DCV, three to OMB, two to DSB, two to SIM, two to SOF, two to PTV/RTV, and one to SOF/LDV (Table 5).

Table 2. Enzyme inhibition drug interactions related to HCV drugs

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Anesthetic/benzodiazepine			
MDL (13)	SIM	2: high risk	MDL's AUC increased 1.45 times after concomitant use with SIM. Monitor parameters of effectiveness and safety of MDL due to its narrow therapeutic margin, dose adjustment may be necessary.
MDL (22)	FDV	2: high risk	240 mg of FDV 2 times/day increases systemic exposure (AUC and Cmax) to MDL (CYP3A substrate) 192% and 104% as a result of hepatic and intestinal CYP3A inhibition. Monitor and adjust the dose of MDL.
Antibiotic/Macrolide			
Erythromycin (13)	SIM	1: very high risk	AUC increased up to 7.47 times and AUC of the macrolide increased up to 1.90 times due to the inhibition of CYP3A4 and Gp-p. Concomitant use is not recommended, the combination is contraindicated.
Contraceptives			
Ethinyl estradiol and norgestimate /NOR (23-25)	PTV/RTV, OMB + DSB	1: very high risk	Joint administration generated changes in exposure to PTV. Its Cmax increased 24% and its AUC increased 23%. NGMN, a metabolite of norgestimate, increased the Cmax by 101% and the AUC by 160%. NG, another metabolite, increased Cmax by 126% and AUC by 154%. The AUC of EE also increased 22% while that of NOR increased 29%. ALT levels increased from 3 to 4 times. Co-administration is contraindicated due to the potential for increasing ALT levels.
Azole antifungals			
KCZ (7, 26)	ASV	2: high risk	KCZ is a potent inhibitor of Gp-p and CYP3A4, which increases the AUC of ASV (substrate of Gp-p and metabolized via CYP3A4) from 7 to 10 times. Monitor ASV safety parameters; a dose adjustment is recommended.
KCZ (27)	PTV/RTV, OMB	2: high risk	Increases AUC by 105%, increases Cmax of PTV exposure by 72% and AUC of PTV exposure by 116%. Limit the dose of KCZ to 200 mg/day.
KCZ (7, 24, 25, 28, 29)	PTV/RTV, OMB + DSB	2: high risk	There is an increase in exposure to KCZ: Cmax increases 37% and AUC increases 117%. T1/2 increases more than 4 times (up to 15.7 times) due to inhibition by CYP3A4. In addition, the AUC of PTV doubles, its Cmax increases 16% and its AUC increases 42%. The dose of KCZ should not exceed 200 mg/day for patients being treated for HCV. 3D treatment and azole antifungals should be used with caution.
KCZ (30)	VEL	2: high risk	KCZ is a potent inhibitor of CYP3A4 and Gp-p and slightly inhibits CYP2C8. VEL is a substrate of Gp-p and is affected by inhibitors of CYP3A4 and CYP2C8. Co-administration increased the AUC of VEL by 70% and its by 29%. T1/2 increased from 16.9 to 23.7 hours. Requires monitoring and dose adjustment.
Antihypertensive drugs/CCB			
Amlodipine (25, 28, 29)	PTV/RTV, OMB + DSB	2: high risk	The Cmax of amlodipine, a CYP3A4 substrate, increased 26% and its AUC increased 157% while the Cmax of PTV decreased by 23% and its AUC decreased 22%. It is recommended to reduce the dose of CCB by half (50%) with clinical monitoring.
ARV/CCR5 antagonist			
MVC (31)	PTV/RTV, OMB + DSB	2: high risk	Simultaneous administration could increase plasma levels of MVC, a CYP3A4 substrate. ARV may need dose adjustment after concomitant use, because RTV is a potent CYP3A4 inhibitor.

Table 2. Enzyme inhibition drug interactions related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
ARV/CCR5 antagonist			
Elvitegravir/c/emtricitabine/ TDF (31, 32)	PTV/RTV, OMB + DSB	1: very high risk	Plasma levels of the anti-HCV scheme are expected due to the inhibitory effect of c on CYP3A4. Concomitant use is not recommended, both regimens contain pharmacokinetic reinforcement; contraindicated.
Elvitegravir/c/emtricitabine/ TDF (31, 33, 34)	SIM	1: very high risk	C increases plasma levels of SIM by interaction via CYP3A4 which increases the possibility of supratherapeutic effects. Concomitant use is not recommended.
ARV/PI			
ATV/RTV (7, 10, 16, 32-38)	DCV	2: high risk	Exposure to DCV increased from 2.1 to 3 times (110%) due to CYP3A4 inhibition. Reduce the dose of DCV from 60 to 30 mg if the DAA is co-administered with potent CYP inhibitors.
DRV/RTV (33-37)	DCV	2: high risk	Exposure to DCV increased 1.4 times due to CYP3A inhibition by DRV/RTV. Reduce the dose of DCV from 60 to 30 mg if co-administered with potent CYP inhibitors.
RTV (39)	DNV	2: high risk	Cmax of DNV 2 increased 40% and its AUC increased 73%. Effect of RTV can involve not only the inhibition CYP450 but also the inhibition of transporters involved in gastrointestinal absorption (first-pass effect). Monitor DNV, a dose adjustment may be necessary.
ATV/RTV (36)	EBR	2: high risk	EBR's AUC increased by up to 376% after use with ATV boosted by RTV. DAA safety parameters must be monitored. A dose adjustment may be necessary.
DRV/RTV (36)	EBR	2: high risk	EBR's AUC increased by 66% after joint use with DRV enhanced with RTV. The DAA safety parameters must be monitored. A dose adjustment may be necessary.
LPV/RTV (36)	EBR	2: high risk	EBR's AUC increased 271% after concomitant administration with LPV enhanced with RTV. Joint use is not recommended. DAA safety parameters must be monitored. A dose adjustment may be necessary.
ATV/RTV (36)	GZR	1: very high risk	GZR's AUC increased by up to 958% after being administered with ATV boosted by RTV. Due to the significant increase in exposure to GZR, it is necessary to suspend concomitant use and avoid unwanted toxic effects.
DRV/RTV (36)	GZR	1: very high risk	GZR's AUC increased by 650% when it was administered with DRV/RTV. Due to the significant increase in exposure to GZR it is necessary to suspend concomitant use and avoid toxic effects.
LPV/RTV (36)	GZR	1: very high risk	GZR's AUC increased 1,186% when it was administered with LPV enhanced with RTV. Due to the significant increase in exposure, it is necessary to suspend use and avoid unwanted toxic effects.
Fosamprenavir/RTV (5, 31, 32)	PTV/RTV, OMB + DSB	2: high risk	Simultaneous administration could increase plasma levels of the anti-HCV scheme. Concomitant use is not recommended. PIs should not be reinforced with RTV in 3D treatment since it contains 100 mg of RTV.
ATV (10, 29, 35-37, 40)	PTV/RTV, OMB + DSB	2: high risk	PTV's AUC increased 94%, its Cmax increased 46%, and its Cmin increased 226%. Nighttime administration increased PTV exposure to 1,095%. ATV's Cmax and AUC increased by as much as 19%. When ATV is administered at night, it increases the Cmin 68%. There is a risk of hyperbilirubinemia. Use is not recommended, unless the PI is enhanced with RTV. Monitor safety parameters, adjust doses, and monitor administration conditions.
LPV/RTV (3, 5, 10, 14, 16, 29, 31, 32, 37, 40)	PTV/RTV, OMB + DSB	1: very high risk	PTV's AUC increased 119% and its Cmax increased 216 % due to CYP3A inhibition and cumulative dose of RTV (300 mg). When administered 1 time/day, the AUC of PTV increased 87% and its Cmin increased 723%. When administered twice a day the Cmax increased 104%, the AUC increased 117%, and the Cmin increased 136%. Concomitant use is contraindicated. Accumulation of doses of RTV with 3D is not recommended since it contains 100 mg of RTV.
Saquinavir/RTV (5, 31, 32)	PTV/RTV, OMB + DSB	2: high risk	Joint administration could increase PTV plasma levels so is not recommended. PIs should not be reinforced with RTV in 3D treatment since it contains 100 mg of RTV.

Table 2. Enzyme inhibition drug interactions related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
ARV/PI			
Tipranavir/RTV (5, 31, 32)	PTV/RTV, OMB + DSB	2: high risk	Simultaneous administration could increase plasma levels of the anti-HCV scheme so is not recommended. PIs should not be reinforced with RTV in 3D treatment since it contains 100 mg of RTV.
ATV/RTV (16, 24, 31, 34, 41, 42)	SIM	1: very high risk	Concomitant use of PI with SIM could significantly increase SIM PC due to inhibition of CYP3A4. SIM administration with any HIV PI, with or without RTV, is not recommended.
DRV/RTV (10, 13, 16, 24, 31, 34, 36, 37, 41, 42)	SIM	1: very high risk	DRV/RTV increases SIM's AUC by 159%, increases its by 180%, and increases its Cmin by 460% due to inhibition of CYP3A4. Concomitant use of PI, with or without RTV, is not recommended.
Fosamprenavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Concomitant use of PIs, whether or not they are boosted, and SIM could significantly increase SIM PC by inhibition of CYP3A4. Concomitant use is not recommended.
LPV/RTV (24, 31, 41, 42)	SIM	1: very high risk	Significant increase in SIM PC enables adverse effects to arise at lower doses than therapeutic doses. The concomitant use of these drugs is not recommended.
Nelfinavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Significant increase in SIM PC enables adverse effects to arise at lower doses than therapeutic doses. The concomitant use of these drugs is not recommended.
RTV (3, 13, 24, 31, 34, 41, 42)	SIM	1: very high risk	RTV increases the AUC of the SIM by 618%. RTV is a potent CYP3A enzyme inhibitor whereby SIM is metabolized. The SIM safety profile must be monitored, concomitant use is not recommended.
Saquinavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Administration of enhanced PI plus SIM could significantly increase SIM levels due to CYP3A4 inhibition. Do not administer SIM with any PI, with or without RTV.
Tipranavir/RTV (24, 31, 41, 42)	SIM	1: very high risk	Administration of PI enhanced with RTV plus SIM could significantly increase SIM PC. Concomitant use of SIM with PI, enhanced or not, is not recommended.
ARV/NNRTI			
Rilpivirine (10, 14, 16, 24, 29, 31, 32, 34, 36, 37)	PTV/RTV, OMB + DSB	1: very high risk	Rilpivirine levels increase 3.25 times with increased risk of elevating QT interval. AUC, Cmax and Cmin increase 225%, 155% and 262%, respectively. AUC and Cmax of PTV increase 23% and 30%, respectively. AUC and Cmax of OMB increase 9% and 11%, AUC and Cmax of DSB increase 17% and 18%. It is not recommended; contraindicated.
EFZ (14, 16, 24, 29, 32)	PTV/RTV, OMB + DSB	1: very high risk	Liver enzymes increase and neurological and gastrointestinal side effects of EFZ worsen. ARV exposure increases more than 200%. Concomitant use is not recommended; contraindicated.
Delavirdine (16, 24, 41)	SIM	1: very high risk	Plasma levels of SIM could increase due to CYP3A4 inhibition exposing the patient to possible adverse effects from doses higher than therapeutic ones. The concomitant use of these drugs is not recommended.
Tuberculosis Treatment			
RFP (26)	ASV	1: very high risk	RFP increases the AUC of ASV 14.8 times. Their joint use is not recommended due to toxicity and possible increase in ALT; contraindicated.
DAA/NS5A protein inhibitor			
DCV (13)	SIM	2: high risk	Plasma levels of both drugs increased, the Cmax of DCV increased 1.50 times and that of SIM increased 1.39 times. Monitor safety of drugs, dose adjustment may not be necessary.
Special Conditions			
Moderate/severe hepatic impairment (7, 17, 19, 26, 32)	ASV	1: very high risk	In Child-Pugh B and C liver failure, ASV increased its Cmax 5 to 10 times and its AUC 23 to 32 times. There is a risk of hepatotoxicity. Use is contraindicated; if used, requires monitoring of therapeutic safety.
Moderate hepatic impairment (6, 7, 10, 17, 28, 43)	PTV/RTV, OMB + DSB	2: high risk	Administration of 3D caused the AUC of PTV to increase 62%, while those of OMB, DSB and RTV decreased more than 30%. Use is not recommended, monitor safety parameters.

Table 2. Enzyme inhibition drug interactions related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Special Conditions			
Severe hepatic impairment (6, 7, 10, 17, 19, 28, 43)	PTV/RTV, OMB + DSB	1: very high risk	The AUC of DSB increases 325%, and the AUC of PTV increases 920% while the AUC of OMB decreases 55%. The use of 3D in severe hepatic impairment is contraindicated by significant increases and decreases in exposure to DAAs.
Moderate/severe hepatic impairment (4, 7, 10-13, 17, 19, 20, 32)	SIM	2: high risk	Since SIM is mainly metabolized in the liver, use in this condition can lead to drug accumulation. The AUC of SIM increases 2.4 to 5.2 times in in hepatic insufficiency classes B and C. Do not use due to the risk of hepatotoxicity, monitor safety parameters and adjust the dose. Patients with class C cirrhosis should be referred for transplantation. If transplantation is not an option, the recommended therapy is 48 weeks of SOF/RBV.
Hypolipidemic and Antilipidemic Drugs			
GFB (25, 28, 29)	PTV/RTV, OMB + DSB	1: very high risk	GFB with 3D inhibits CYP2C8. PTV's Cmax increases by 21%, and its AUC increases 38%. The Cmax of DSB increases 101% while its AUC increases 1,030%. T1/2 increased from 5 to 90 hours resulting in risk of prolongation of the QT interval. Concomitant use is contraindicated.
Immunosuppressants			
TAC (19, 44)	DCV	2: high risk	The concentration of TAC increased the first 2 weeks after starting DCV, but this ratio decreased from the third week. Therapy should be monitored and the dose adjusted according to the increase in exposure.
CsA (39)	DNV/RTV	2: high risk	CsA (39) DNV/RTV 2: high risk DNV's AUC increased 14 times and its Cmax increased 7 times after co-administration of the calcineurin inhibitor. The use of ADR enhanced with RTV plus CsA increases DNV exposure significantly. Monitoring and dose adjustment are required.
CsA (3, 7, 10, 15, 19, 24, 29, 31, 45-48)	PTV/RTV, OMB + DSB	2: high risk	The AUC of CsA increased 482%, and there was a 2-fold increase in the AUC of PTV. At the beginning of therapy, the dose of CsA should be reduced to 20% of the current dose, the PC should be measured to determine subsequent modifications. Once 3D therapy is complete, the dose of CsA should be guided by blood concentration assessment. Frequent evaluation of renal function and side effects is recommended.
Mycophenolate mofetil (31)	PTV/RTV, OMB + DSB	2: high risk	Joint administration increased mycophenolate levels. Monitor the safety parameters of mycophenolate mofetil. A dose adjustment may be necessary.
TAC (14, 15, 19, 31, 45, 46, 48)	PTV/RTV, OMB + DSB	1: very high risk	Joint administration of 3D and TAC increased the AUC of TAC 57.1 times due to CYP3A4 inhibition. Do not use together. If they are used together, monitor therapy and adjust the dose or time of administration. If RTV is used, use immunosuppressive therapy with CsA with TAC as the first choice.
SRL (31)	PTV/RTV, OMB + DSB	1: very high risk	Plasma levels of SRL increase: Cmax increases by 6.4 times, AUC by 38.0 times and Cmin by 19.6 times due to CYP3A4 inhibition. Co-administration is contraindicated unless the benefits outweigh the risks in which case the dose should be adjusted.
TAC (24, 47)	PTV/RTV, OMB	1: very high risk	Enzymatic inhibition of TAC via CYP3A4 evidenced by increase of AUC by 5613%. The simultaneous use of these drugs is contraindicated.
CsA (3, 7, 10, 11, 13, 14, 19, 24, 31, 42, 45, 47-50)	SIM	1: very high risk	SIM PC can increase up to 6 times when administered with CsA. There is a 4.74 fold increase in AUC due to the inhibition of CYP3A, Gp-p and OATP 1B1. Joint use is contraindicated.
TAC (7, 10, 13, 24, 31, 45, 48, 49, 51)	SIM	2: high risk	SIM exposure was not significantly altered, Cmax and AUC increased by 1.8 and 1.9 times, respectively. AUC and Cmax of TAC decreased by 17% and 24%, respectively. Therapeutic effectiveness and safety should be monitored. A dose adjustment may be necessary.

AUC: area under the curve; ALT: alanine transaminase; ARV: antiretroviral; ATV: atazanavir; CCB: calcium channel blocker; c: cobicistat; CCR5: type 5 receptor chemokine; Cmax: maximum concentration; Cmin: minimum concentration; PC: plasma concentration; CsA: cyclosporine; CYP: cytochrome P450; CYP2C8: cytochrome P450 2C8; CYP3a4: cytochrome P450 3A4; DRV: darunavir; EE: ethinylestradiol; GFB: gemfibrozil; Gp-p: glycoprotein p; IP: protease inhibitor; NNRTI: Non-nucleoside reverse-transcriptase inhibitors; KCZ: ketoconazole; LPV: lopinavir; MDL: midazolam; MVC: maraviroc; NG: norgestrel; NGMN: norelgestromin; NOR: norethindrone; RFP: rifampicin; SRL: sirolimus; TAC: tacrolimus; t1/2: average life time; TDF: tenofovir disoproxil fumarate; 3D: PTV/RTV/OMB + DSB.

Table 3. Drug interactions induced by enzymes related to HCV drugs

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Anticonvulsants			
CBZ (carbamazepine) (23-25, 28, 29)	PTV/RTV, OMB + DSB	1: very high risk	Induction of CYP3A by CBZ affects 3D by decreasing exposure of DAA: the Cmax of PTV decreases by 66%, and its AUC decreases by 70% (decrease in exposure up to 87%); the Cmax of DSB decreases by 55% and its AUC by 70% (decrease in exposure up to 87%); and the Cmax of OMB decreases by 31% while is AUC decreases by 30%. The results are losses of antiviral activity and therapeutic effectiveness. Concomitant use of these drugs is contraindicated.
ARV/IP			
DRV (16, 24, 29, 31, 34-36, 40)	PTV/RTV, OMB + DSB	2: high risk	3D therapy can reduce plasma DRV levels and cause therapeutic ineffectiveness. The AUC of DRV decreased by 24% and its Cmax decreased by 48%. In addition, DAAs decreased. The AUC of PTV decreased 41%, its Cmax decreased 30% (decrease up to 59%); the AUC of DSB decreased between 27% and 53%; and the AUC of OMB decreased 27%. The effectiveness parameters of the therapies should be monitored. A dose adjustment may be necessary.
ARV/NNRTI			
EFZ (6, 7, 10, 16, 33, 34, 36-38)	DCV	2: high risk	EFZ decreases the AUC of DCV from 32% to 50% by induction of CYP3A4, but the interaction's significance is unknown. The parameters of therapeutic effectiveness should be monitored, and the dose of DCV should be increased to 90 mg/day.
Nevirapine (10, 16)	DCV	2: high risk	Nevirapine lowers plasma levels of DCV possibly via CYP3A4. Increasing the dose of DCV is required. There are no recommendations to avoid concomitant use.
Etravirine (31)	PTV/RTV, OMB + DSB	2: high risk	Co-administration of these drugs leads to decreased plasma levels in the 3D scheme. Concomitant use of these drugs is not recommended.
EFZ (36)	EBR	2: high risk	EBR's AUC decreases 54% when administered with EFZ, a known enzyme inducer. Effectiveness parameters should be monitored. A dose adjustment may be necessary.
EFZ (35, 36)	GZR	2: high risk	GZR's AUC decreased 84% when administered with EFZ. The parameters of therapeutic effectiveness should be monitored and the dose of GZR adjusted if necessary.
Nevirapine (31)	PTV/RTV, OMB + DSB	2: high risk	Joint administration decreases the plasma levels of the anti-HCV scheme and could increase the plasma levels of nevirapine. Joint administration is not recommended.
EFZ (10, 13, 16, 24, 31, 33-37, 42)	SIM	1: very high risk	This NNRTI lowers plasma SIM levels. AUC, Cmax and Cmin decreased 71%, 51% and 91%, respectively, due to CYP3A induction. Concomitant use is contraindicated and not recommended.
Etravirine (16, 24, 31, 33, 42)	SIM	2: high risk	This NNRTI can decrease SIM PC by induction of CYP3A which leads to therapeutic failure. Monitor effectiveness parameters. They should not be administered together.
Nevirapine (16, 24, 31, 42)	SIM	2: high risk	This NNRTI can lower plasma SIM levels and lead to therapeutic failure. Monitor effectiveness parameters. Joint administration is not recommended.
Tuberculosis Treatments			
RFP (13, 42)	SIM	2: high risk	SIM's AUC is decreased by 48% due to induction of CYP3A4 and inhibition of OATP 1B by RFP. Monitor therapeutic effectiveness and adjust the dose of SIM. Concomitant use is not recommended.
RFP (30)	VEL	2: high risk	RFP induces CYP3A4 and is a potent OATP inhibitor. VEL is a OATP substrate and inhibitor as well as a CYP3A4 substrate. Concomitant use of these drugs and multiple doses of RFP decrease VEL exposure. Its AUC decreased by 82%, and its Cmax decreased by 711%. In addition, T1/2 went from 18.0 to 11.7 hours. Monitor and adjust dose.
Special Conditions			
Severe hepatic impairment (17)	OMB	2: high risk	AUC of OMB decreases by as much as 54%. Use of OMB is not recommended. Monitor effectiveness of therapy and adjust dose.

Tabla 3. Interacciones medicamentosas por inducción enzimática relacionadas con medicamentos en el tratamiento del VHC (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Immunosuppressants			
CsA (19)	IFN	2: high risk	CsA's PC decreases due to increased calcineurin inhibitor metabolism. Monitor effectiveness of immunosuppressant. A dose adjustment may be necessary.
TAC (19)	IFN	2: high risk	TAC's PC decreases due to increased calcineurin inhibitor metabolism. Monitor effectiveness of immunosuppressant. A dose adjustment may be necessary.
Natural products			
St. John's Wort (28, 29)	PTV/RTV, OMB + DSB	2: high risk	Co-administration of 3D with natural products can decrease DAA exposure due to potent induction of CYP3A4. Co-administration is not recommended, and use is not indicated. If used, therapeutic monitoring and dose adjustment are required.

CBZ: carbamazepine; EFZ: efavirenz.

Table 4. Drug interactions due to changes in bioavailability related to HCV drugs

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Hepatoprotective agent			
GCR (52)	PTV/RTV, OMB	2: high risk	2D exposure was not affected. GCR's AUC increased by 49%. No dose adjustment of GCR is required under feeding conditions. Monitor therapeutically.
Antacids			
Aluminum and magnesium hydroxide (53)	SOF/LDV	2: high risk	Acid reducing drugs increase gastric pH which causes decreased LDV absorption. Antacids should be administered 4 hours before or after administration of SOF/LDV.
DIG (7, 42)	LDV	2: high risk	The PC of DIG (Gp-p substrate) increases because LDV is a Gp-p substrate and inhibitor. Monitor plasma DIG levels and consider dose adjustment.
DIG (27)	PTV/RTV, OMB	2: high risk	DIG is a Gp-p substrate while PTV is a potent Gp-p inhibitor. The Cmax and AUC of DIG increase 58% and 36%, respectively. Routinely monitor and reduce the dose of DIG 30% to 50%.
DIG (30)	VEL	2: high risk	DIG is a Gp-p substrate and VEL slightly inhibits this transporter. DIG's AUC and Cmax increase 34% and 88%, respectively. Monitor therapy and reduce the dose of DIG 30% to 50%.
Anticonvulsants			
CBZ (11, 20, 42)	SOF	1: very high risk	CBZ is a potent Gp-p inducer which decreases SOF's PC and its metabolite GS-331007 significantly leading to therapeutic failure. Joint administration is contraindicated.
Antihistamines			
FMT (24, 33, 53)	LDV	2: high risk	Acid reducing drugs such as FMT increase gastric pH causing decreased LDV absorption. PC is reduced by 50%, and viral resistance is of concern. Do not exceed 40 mg of FMT 2 times/day. Antihistamines should be taken within 12 hours of DAAs.
ARV/IP			
DRV/RTV (18, 24, 37, 54)	SOF	2 high risk	DRV/RTV can increase the AUC of SOF to 34%, and its Cmax to 55%. The increase is not considered clinically relevant, but safety parameters of the SOF should be monitored.
ATV/RTV + emtricitabine/TDF (34, 36)	SOF/LDV	2: high risk	Minimum levels of TDF increase between 40% and 60%, and ATV's PC increases by 63%. TDF levels are already increased between 20% and 30% by co-administration with the IP enhanced with RTV regardless of the DAA. Joint use is not recommended and should be avoided due to nephrotoxicity.

Table 4. Drug interactions due to changes in bioavailability related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
ARV/IP			
DRV/RTV + emtricitabine/TDF (34, 36)	SOF/LDV	2: high risk	Plasma TDF levels increase 40% to 60%, and LDV's AUC and Cmax increase 90% and 134%, respectively. TDF levels are already increased between 20% and 30% by co-administration with the DRV/RTV regardless of the DAA. Avoid use due to renal toxicity and indirect hyperbilirubinemia.
PPIs			
OMZ (24, 33, 53)	LDV	2: high risk	OMZ increases gastric pH and decreases LDV absorption. PC is reduced by approximately 50% and viral resistance can be worrisome. LDV's effectiveness should be monitored. OMZ should be used at doses <20 mg/day, 2 hours before or after administering the DAA.
ARV/Integrase inhibitor			
RAL (55)	FDV	2: high risk	FDV is a weak inhibitor of CYP3A4, Gp-p and UGT 1A1 which intervenes in the clearance of RAL, a substrate of Gp-p. Joint use increased the AUC and Cmax of RAL and its glucuronide metabolite 2.7 and 2.5 times, respectively. Monitor the safety profile of RAL, a dose adjustment may be necessary.
Tipranavir/RTV (3, 10, 16, 24, 31, 34, 42, 54, 56)	SOF/LDV	2: high risk	Tipranavir boosted with RTV can lower the PC of SOF and LDV (substrates of Gp-p) by induction of Gp-p. Joint administration should be avoided given the risk of viral susceptibility and development of resistance from sub-therapeutic levels of the drug. Monitor therapeutic effectiveness. A dose adjustment may be necessary.
ARV/NRTI			
Zidovudine/lamivudine/EFZ (41, 57)	SOF	2: high risk	SOF's Cmax decreases 49% due to induction of Gp-p and BCRP. Changes in exposure are modest but may require dose adjustment.
Emtricitabine/TDF/EFZ (14, 31, 34, 36, 37, 56)	SOF/LDV	2: high risk	TDF's AUC increases 98% and LDV's PC decreases 30%. Inhibition of the Gp-p and BCRP has been reported. Monitor renal function. Dose adjustment may be required.
Emtricitabine/TDF/rilpivirine (31, 34, 36, 37)	SOF/LDV	2: high risk	TDF's AUC increases 40% due to inhibition of Gp-p and BCRP. Monitor renal function if DAA therapy with TDF is administered. Dose adjustment may be needed.
TDF/GFR <60 mL/min (16)	SOF/LDV	2: high risk	LDV increases TDF's PC and, depending on decrease in the value of the GFR, may increase the risk of nephrotoxicity. Use is not recommended. Any use requires clinical monitoring and dose adjustment.
Tuberculosis Treatment			
RFB (11, 42)	SOF	2: medium risk	RFB induces Gp-p and can significantly decrease SOF's PC and lead to therapeutic failure. Administration is not recommended due to expected therapeutic ineffectiveness.
RFP (18, 20, 33, 42, 57)	SOF	1: very high risk	RFP is a potent Gp-p inducer. When combined with SOF, RFP's AUC decreases 72% and its Cmax decreases 77%. The use of RFP with powerful Gp-p inductors is contraindicated.
RFP (30)	VEL	2: high risk	RFP is a potent OATP inhibitor, VEL is a substrate and inhibitor of the same transporter. Joint administration increases exposure to VEL: AUC increases 47%, Cmax increases 28%. The safety of the VEL should be monitored and the dose adjusted.
Hypolipidemic drugs (Statins)			
RVS (7, 42, 54)	LDV	2: high risk	Plasma levels of RVS increase. LDV is a substrate and weak inhibitor of Gp-p and BCRP while RVS is a substrate of BCRP. Monitor the safety profile of the RVS, a dose adjustment may be necessary.
PRA (7, 23, 25, 28)	PTV/RTV, OMB + DSB	2: high risk	There is a 2-fold increase in exposure to PRA (OATP substrate 1B1/B3), Cmax and AUC increased 37% and 82% due to inhibition of OATP 1B1/B3 by PTV. Reduce the PRA dose by half when administered together with 3D therapy. Do not exceed 40 mg/day of PRA.

Table 4. Drug interactions due to changes in bioavailability related to HCV drugs (*continued*)

Pharmacological group or drugs related to interaction	HCV Drug	Level of clinical relevance	Comments and suggestions
Hypolipidemic drugs (Statins)			
RVS (3, 7, 23, 25, 28)	PTV/RTV, OMB + DSB	2: high risk	Exposure to RVS, a substrate of OATP and BCRP, increases: AUC increased 159% and Cmax increased 613%. The AUC and Cmax of PTV increased 52% and 59%, respectively. The dose of RVS should be adjusted. A dose of 10 mg/day is suggested.
PRA (27)	PTV/RTV, OMB	2: high risk	PRA is a substrate of OATP 1B1/B3 while PTV is an inhibitor of the same transporter. Joint use increased the Cmax of PRA 43%, and its AUC 76%. Those of PTV increased by 44% and 33%, respectively. The dose of PRA should be halved and the safety profile monitored.
RVS (27)	PTV/RTV, OMB	2: high risk	RVS is a substrate of OATP 1B1/B3 and BCRP while PTV is an inhibitor of these transporters. Joint use increases exposure to RVS: Cmax increases 161%, and AUC increases 33%. The Cmax and AUC of PTV increased by 40% and 22%, respectively. The dose of RVS should be halved and should not exceed 20 mg/day.
RVS (3, 7)	SIM	2: high risk	Joint use increases exposure to RVS: Cmax and AUC increased 3.17 and 2.81 times, respectively, due to inhibition of OATP 1B1. Restrict the dose of RVS to 10 mg/day when combined with SIM.
AVA (3, 7)	SIM	2: high risk	Exposure to VPA increases: AUC increased 2.2 and Cmax increased 1.7 times due to inhibition of OATP 1B1. Restrict the maximum dose to 40 mg/day when combined with SIM. Use the minimum dose necessary when the safety profile is affected.
PRA (30)	VEL	2: high risk	PRA is a substrate of OATP 1B1 while VEL is a substrate and inhibitor of this transporter. Co-administration increased PRA's AUC by 35% and its Cmax by 28%. It is necessary to monitor the safety profile of the lipid lowering agent and adjust the dose if necessary.
RVS (30)	VEL	2: high risk	RVS is a substrate of BCRP while VEL is a moderate inhibitor of this transporter in the intestines. Co-administration increased RVS's AUC by 170% and its Cmax by 160%. The safety of the RVS should be monitored and the dose adjusted if necessary.
Immunosuppressants			
SRL (31)	SOF/LDV	2: high risk	Concomitant use can significantly increase the PC of SRL. The safety profile of SRL must be monitored, and dose adjustment may be necessary.
CsA (19, 58)	SOF/RBV	2: high risk	CsA's PC decreases due to an increase in metabolism. Drugs administered concomitantly should be monitored, and a dose adjustment may be necessary.
TAC (19, 58)	SOF/RBV	2: high risk	CT's PC decreases due to the increase in metabolism. Drugs administered concomitantly should be monitored, and a dose adjustment may be necessary.
CsA (30)	VEL	2: high risk	CsA is a potent inhibitor of Gp-p while VEL is a substrate and a mild inhibitor of this transporter. Co-administration increased the AUC of VEL by 103% and its Cmax by 56%. The safety of VEL must be monitored, and a dose adjustment may be necessary.
Natural products			
St. John's Wort (18, 20, 33, 42, 57)	SOF	1: very high risk	SOF's PC decreases after concomitant use of this natural product, the mechanism of interaction is thought to be induction of Gp -p. They should not be used together due to possible therapeutic ineffectiveness.

AVA: atorvastatin; DIG: digoxin; FMT: famotidine; GCR: glycyrrhizin; PPI: proton pump inhibitor; NRTI: nucleoside analogue reverse transcriptase inhibitor. OMZ: omeprazole; PRA: pravastatin; RAL: raltegravir; RFB: rifabutin; RVS: rosuvastatin; GFR: glomerular filtration rate; UGT: Glucuronosyltransferase; 2D: PTV/RTV.

Table 5. Drugs with evidence of absence of clinically relevant interactions

Pharmacological group or drugs related to interaction	HCV Drug	Pharmacological group or drugs related to interaction	HCV Drug
Analgesic Opioid		**ARV /Integrase Inhibitor**	
Methadone (26) Buprenorphine (26)	ASV	RAL (13, 24)	SIM
		ARV/NNRTI	
Methadone (59) Buprenorphine (12, 59)	DCV	Rilpivirine (24)	SOF
		Rilpivirine (24)	LDV
Methadone (59) Buprenorphine (59)	DSB	**ARV/NRTI**	
		TDF (24)	DCV
Methadone (54, 59) Buprenorphine (54, 59)	LDV	TDF (24, 54)	LDV
		Emtricitabine/TDF (24)	OMB
Methadone (59) Buprenorphine (59)	OMB	**PPI**	
		OMZ (31)	ASV
Methadone (59) Buprenorphine (59)	PTV/RTV	**AAD**	
		DCV (26)	ASV
Methadone (54, 59) Buprenorphine (54, 59)	SOF	**Special Condition**	
		Decompensated Cirrhosis (31)	SOF/LDV
Buprenorphine (59)	SIM		
Antidepressant/SSRI		**CNS stimulant**	
Escitalopram (26)	ASV	Caffeine (26)	ASV
Sertraline (26)	ASV	**Immunosuppressants**	
Antihypertensive/ARA II		CsA (24, 42, 47, 54, 60)	LDV
Losartan (26)	ASV		

ARA II: angiotensin II receptor antagonist; SSRI: selective serotonin reuptake inhibitor; CNS: central nervous system.

DISCUSSION

Some HCV patients may have comorbidities that compromise their health status, among them HIV and hepatitis B virus (HBV) stand out for the similarity of their routes of infection. Other common comorbidities include dyslipidemia, arterial hypertension, diabetes, and arthritis typical of the passage of age. (28, 61) The emergence of new DAAs means that health professionals should be attentive to possible drug interactions, since DAAs' pharmacokinetic profiles involve isoenzymes, transporters and mechanisms that are shared with other medicines. This can contribute to development of drug-related problems thereby increasing the risk of adverse events. Consequently, continuous review of clinically relevant interactions with DAA related to HCV treatment is important for avoiding risks that alter the safety and effectiveness of treatment. (62)

This review identified 155 pairs of interactions: thirty-four (21.9%) were level 1, seventy-three (47.1%) were level 2, and forty-eight (31.0%) were level 3. One hundred fifty-four (99.4%) of these were pharmacokinetic, a finding similar to those of other reviews which have found that more than 90.0% of reported drug interactions were pharmacokinetic. Similarly, the most common mechanisms were enzyme inhibition and enzyme induction. This is a strong indication that clinicians should evaluate concomitant pharmacotherapy in cases where drugs used can affect enzymatic activity of the CYP450 complex. (37) Assessment of clinical relevance is based on severity and probability of an interaction occurring. (9) This method is one of the strengths of this review with respect to similar reviews since it allows identification of levels of drug interaction severity which can be used to discriminate among pharmacological choices. (10, 59, 63) In addition, 29 pairs of drugs with evidence of absence of clinically relevant interaction were identified.

Compared to our previous review of drug interactions in HCV patients,(8) there are 27 additional pairs of drug interactions that are the result of the development and marketing of new DAAs. IN that earlier review, pharmacokinetic drug interactions accounted for 93.7% of these pairs. Enzyme inhibition accounted for 64.0%, enzyme induction

accounted for 27.3%, changes in bioavailability accounted for 2.4%, pharmacodynamic interactions accounted for 6.3%. Drug interactions identified by the enzyme inhibition mechanism decreased by 12 in this new review while drug interactions identified by the enzyme induction mechanism decreased by 10. These were attributed to different DAAs since boceprevir and telaprevir have fallen out of use. On the other hand, drug interactions identified by changes in bioavailability increased 33.8% because the pharmacokinetic profiles of the new DAAs include carriers such as OATP, Gp-p and BCRP. (7, 29, 36, 50, 53 , 64) Pharmacodynamic interactions decreased 5.7% because of the greater number of interactions with RBV associated with mitochondrial toxicity, lactic acidosis and hematological toxicity identified during concomitant use with NRTI, telaprevir, boceprevir and IFN in the previous review. (8)

The 3D therapy composed of PTV/RTV, OMB + DSB presented 34 drug interactions. Of these, 24 (70.6%) were due to enzymatic inhibition, six (17.6%) were due to induction, and four (11.8%) were due to changes in bioavailability. These interactions were mainly due to the drugs' pharmacokinetic profiles since the drugs that make up 3D therapy are substrates and inhibitors of Gp-p and BCRP. In addition, PTV is an OATP substrate. PTV is a substrate of CYP3A4 while OMB is metabolized by hydrolysis, DSB is metabolized by CYP2C8 and, to a lesser extent, by CYP3A4. For its part, RTV is used as a pharmacokinetic enhancer of PTV. (29, 36)

Although SOF is a prodrug that does not inhibit or induce the CYP450 complex or transporters, it is also a substrate of Gp-p and BCRP. This is metabolized in hepatocytes into a pharmacologically active nucleoside (GS-461203 triphosphate analog) and in greater proportion (> 78%) to the circulating inactive metabolite (GS-331007). (50, 53) Due to its pharmacokinetic profile, few clinically relevant interactions with the SOF are expected, although it is recommended that concomitant use with strong Gp-p inducers such as RFP and some natural products such as St. John's wort be avoided. On the other hand, SOF can be safely administered with immunosuppressants. (50) In combination with LDV, SOF can be used safely with most ARVs although there is some risk of hyperbilirubinemia when administered with ATV. (37)

The results of this review suggest that clinically relevant interactions with DAAs can be related to multiple mechanisms. Among them, interactions between DAAs with certain morbidities of clinical interest such as cirrhosis, renal failure and inflammatory infectious processes are evident. (32, 65) Liver and kidney damage alters the metabolism and excretion of drugs and their metabolites. This can lead to accumulation of the metabolites in the bloodstream and to possible unwanted toxic effects. Therefore, it is important to constantly monitor therapy and promote rational use of drugs to ensure the best possible health outcomes.

CONCLUSIONS

According to the results obtained, more than 99% of the drug interactions of clinical relevance in HCV patients receiving pharmacological therapy are pharmacokinetic and are associated with either induction or inhibition of liver metabolism and changes in the bioavailability of drugs due to inhibition and/or induction of Gp-p, OATP and BCRP. Clinically relevant interactions may occur frequently in polymedicated patients who receive concomitant therapy for treatment of other associated diseases when they are also receiving SIM or therapies such as 2D and 3D enhanced with RTV. Plasma concentrations of concomitant drugs can be altered in HCV patients being treated with these drugs and drugs for other associated diseases. This situation is more likely in cases where DAAs are administered simultaneously with ARVs, tuberculosis treatments, lipid lowering agents, antiarrhythmic agents, immunosuppressants and anticonvulsants. We recommend looking for the most appropriate therapeutic alternative for each patient's health condition to guarantee effectiveness and safety.

LIMITATIONS

The main limitation of this study was its restricttion to the PubMed/MedLine database. However, this effect was lessened because the review was complemented by a search for bibliographic references found in the 90 articles reviewed.

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Gastric cancer is a preventable disease: Strategies for intervention in its natural history

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Abstract

Gastric cancer is a public health problem, but there are no usable mortality and survival statistics for Colombia. The country has no early diagnosis program or strategy, and gastric cancer is not prioritized as a health problem. Existing studies show that most patients are in advanced stages by the time they are diagnosed.

Ninety percent of gastric cancers are considered to be consequences of long inflammatory processes in the gastric mucosa. H Pylori infections are the most common etiology of gastritis which can progress to atrophy, metaplasia, dysplasia and cancer. Gastric atrophy establishes a cancerization field which is prone to molecular and phenotypic changes that end in cancerous growth. It is well understood that a disease's natural history provides a rational pathological clinical understanding for primary and secondary prevention strategies. Well-established evidence shows that the combination of primary (H pylori eradication) and secondary strategies (diagnosis and endoscopic follow-up of pre-malignant lesions) can prevent or limit the progression of gastric carcinogenesis. The risk of gastric cancer associated with H pylori gastritis can be stratified according to the severity and extent of atrophy of the gastric mucosa. This approach has been adapted to many different countries according to specific incidences of gastric cancer, socio-economic conditions and cultural factors. This requires the complementary participation of gastroenterologists, surgeons, oncologists and pathologists.

In the face of this public health problem, there has been no action by health authorities or the medical association. For this reason, we have reviewed management strategies that allow intervening into the natural history of the disease to reduce its incidence and mortality rate.

The implementation and standardization of these management strategies in our environment may benefit patients who are at high risk for gastric cancer. These strategies can be implemented in a rational way, similar to what is being done with rectal cancer, in countries without screening programs all over the world.

Keywords

Gastric cancer, helicobacter pylori, prevention, natural history.

INTRODUCTION

All around the world, gastric cancer (GC) is a public health problem despite its decreasing incidence and mortality rate. (1) According to GLOBOCAN, 1,033,701 new cases of GC occurred and more than 782,685 deaths due to this disease occurred in 2018. (2) GC represents 5.7% of all new cancer cases and 8.2% of total cancer deaths in the world. (2, 3) Japan and Korea have in the world's highest incidences. High incidence areas are Asia, Eastern Europe, South America and Central America while low incidence areas are South Asia, North and East Africa, North America, Australia and New Zealand. (4) In Japan, where GC remains the most common type of cancer in both men and women, the incidence figures are 69.2/100,000 inhabitants and 28.6/100,000 inhabitants, respectively (4).

According to GLOBOCAN, 7,419 new cases of GC (7.3%) were detected in Colombia in 2018. Of these, 5,505 died. GC ranked third for the year, after breast and prostate cancer. It was followed by lung and colorectal cancer. For

2018, GC represented the first cause of cancer mortality (13.7%). (5)

The risk of developing GC increases with age. It occurs most frequently between the ages of 50 and 80 and is uncommon in people under 30 years of age. (6)

Despite Colombia's significant case load, the country has no GC monitoring and prevention program nor has it prioritized GC as a public health problem. Existing research shows that the majority of GC patients are diagnosed in advanced stages which translates into very low survival figures. (7)

GC is multifactorial with complex interactions of infectious agents such as helicobacter pylori and Epstein-Barr virus; environmental factors including high salt consumption, tobacco consumption and diets poor in fiber, fruit and vegetables; and a genetic component. The most important causative agent is H. pylori, a bacterial infection acquired in childhood. In the absence of adequate treatment, it may persist throughout life and induce a chronic inflammatory response that variably conditions development of atrophy, metaplasia, dysplasia and, finally, GC. (8)

Primary prevention of GC aims at a diet rich in fiber with large amounts of fruit and vegetables plus diagnosis and treatment of H. pylori infection early in life. This strategy must be carried out before atrophy and intestinal metaplasia develop in the gastric mucosa. Secondary prevention aims at diagnosis and monitoring of preneoplastic lesions such as atrophy and intestinal metaplasia using the severity scales of histological staging known as the Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastric Intestinal Metaplasia assessment (OLGIM). (9)

These recommendations are made because screening programs are not possible in countries such as in Colombia with low or intermediate economies where resources must be directed to immediate problems considered of greater urgency. (9)

Unfortunately, in Colombia the diagnosis is made in advanced stages when there is no possibility of cure for this disease. In the face of this public health problem, there has been no action by the health authorities or the medical association. Therefore, proposing strategies to reduce incidence and mortality to the medical community of this country should be an important objective. (9)

GC is a preventable disease. Within the literature there are strategies with adequate levels of evidence that allow action within the disease's natural history to reduce incidence and mortality figures while improving survival through earlier diagnoses. The implementation of these cost-effective management strategies can be achieved in high-risk populations in a rational way similar to how colorectal cancer is being approached. (10)

GENERAL OBJECTIVE

Colombia has no defined policies for controlling and preventing GC. Therefore, the objective of this study is to review intervention strategies aimed at primary and secondary prevention on the basis of our knowledge of GC's natural history with the aim of reducing its incidence while improving mortality and early detection figures.

NATURAL HISTORY

Understanding the natural history of a type of cancer is crucial for designing effective intervention. (11)

In 1975 Pelayo Correa published "A model for the development of gastric cancer" in which he argued that the development of intestinal type GC, the most common subtype, originates in a 30 to 50-year-long process that begins with chronic atrophic gastritis and progresses to intestinal metaplasia, then to dysplasia and finally to cancer. That study postulated that the initial changes occurred in the first decade of life when colonization by H. pylori occurred. Correa initially postulated that the agents responsible for promoting this slow process from gastritis to cancer were related to the environment, based on studies of people migrating from high GC risk areas to low-risk areas. (12)

GC's natural history has three phases: carcinogenic, asymptomatic and clinical or symptomatic (Table 1). (11)

Table 1. Phases of Gastric Cancer

Natural History of GC
Carcinogenic phase
Asymptomatic phase
Symptomatic phase

Carcinogenic Phase (duration of years and decades)

H. pylori gastritis

The most widely accepted hypothesis is that H. pylori is the initial etiological factor of chronic gastritis leading to GC. This infection is acquired in childhood and slowly progresses toward gastric atrophy, intestinal metaplasia, dysplasia and invasive adenocarcinoma of the intestinal type. Its rate of progress varies and is modulated over many years by genetic, dietary and environmental factors which offer broad opportunities for intervention. (11, 12)

In 2002, Bedoya reported that 88% of children under 10 years of age showed some inflammatory changes of the gastric mucosa and changes that 5% presented chronic atrophic gastritis. (13)

A review of gastric biopsies in a population aged one to 16 years by Archila et al. found H. pylori infections in 59% of these patients. There were small quantities of bacteria in 24.3%, moderate quantities in 20.1%, and abundant quantities in 14.6%. (13)

H. pylori is the most important causative agent involved in the genesis of GC. The International Agency for Research on Cancer (IARC) has listed it as a Type I carcinogen since 1994. H. pylori is strongly associated with distal GC of the stomach although no relationship has been demonstrated with GC of the proximal and cardial regions. It has been estimated that more than 75% of gastric cancers worldwide are explained by H. pylori infections. There is also evidence that H. pylori infection is a necessary but not sufficient condition for gastric carcinogenesis. (15)

Other etiological agents such as cigarettes, alcohol consumption and endogenous nitrosamine formation are recognized by the IARC as potential causal factors that in development of GC. Between 11% and 18% of cases may be associated with cigarettes. Diet and nutrition can also play a role in gastric oncogenesis. There is consistent evidence that consumption of fruit and vegetables is associated with decreased risks of GC (Figure 1). (15)

GC's association with family history (genetic component) has an odds ratio (OR) of 2.0 to 8.0, depending on the country. There are also studies that show higher prevalence of H. pylori infections and premalignant lesions in first-degree relatives of GC patients than in controls. (9, 16)

Genetic susceptibility caused by a mutation in E-cadherin, a crucial molecule in maintaining epithelial architecture, is assumed to be related to diffuse GC. (15)

The first crucial event in gastric carcinogenesis is H. pylori infection. It activates the inflammatory response, and there is a high prevalence of H. pylori infections in GC patients. (15) Nevertheless, only a very small proportion of people who are infected patients with H. pylori ever develop GC: only one out of every 100 infected patients will develop GC. (17)

This forces one to wonder why and how the disease develops in this minority of infected patients. One reason is variation in the pathogenicity of the bacteria. Research in this field has focused on genetic susceptibility due to polymorphisms in genes that govern gastric inflammation responses, the heterogeneity of H. pylori, and environmental influences such as salt from the diet or the presence of other species of Helicobacter within the gastrointestinal microbiota. (12)

Considering GC to be the consequence of an infection has created enthusiasm for diagnosing and treating H. pylori in areas of high GC prevalence, (12) and it is clear that most GC is due to H. pylori infections rather than factors related to lifestyles. When it is suspected that cancer is caused by an infection, preventive measures are required in order to reduce both incidence and mortality. (12)

HP infection is typically acquired in childhood, and mucosal transformation takes years and decades to pass through the chronic inflammatory process to states of atrophic gastritis and intestinal metaplasia. Consequently, eradication of the bacteria in young people could prevent this progression and reduce the risk of developing GC later in life. (11)

Based on the arguments, the strategy of diagnosing and treating patients with gastritis associated with H. pylori was validated in Japan in 2009 and 2103 and gained support from

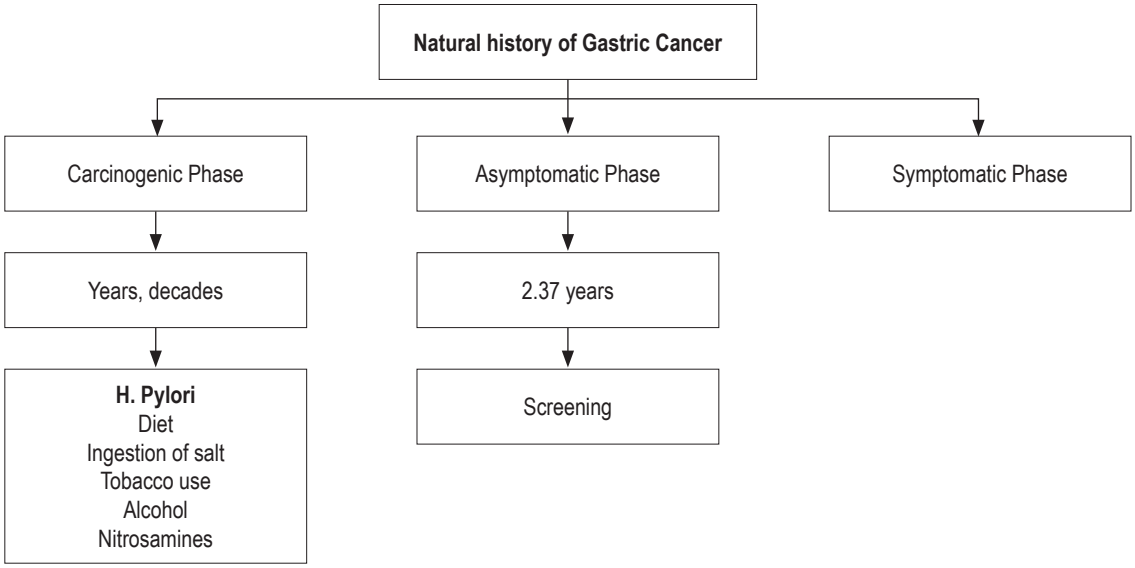

Figure 1. GC risk factors. Taken from: Park JY et al. Clin Endosc. 2014; 47 (6): 478-89.

the health care insurance system. This largest part of this population has non-atrophic gastritis following eradication treatment so endoscopic monitoring is not necessary. (18)

The prevalence of H. pylori is high on the island of Matsú in Taiwan, and the incidence of GC is 50 per 100,000 inhabitants, 3 to 5 times higher than the overall incidence in Taiwan. The age of 30 was chosen as the cut-off for accelerating elimination of GC. A pilot screening study to diagnose and treat H. pylori infections was begun on the island in 2004. Initial results were very promising: incidence of GC decreased by 25% and the incidence of gastric atrophy feel by 77% compared to historical data. (19) It has been calculated that it is necessary to diagnose and treat 15 men in China and 245 women in the United States to avoid one case of GC. (20)

Preventing and eradicating H. pylori infections before atrophic gastritis develops is the best means of reducing and/or eliminating GC. (21)

In 2005, the Nobel Prize in Physiology was awarded to Marshall and Warren for the discovery of H. pylori and its role in gastritis and peptic ulcer. In addition, chronic inflammation is a common risk factor for carcinogenesis, and it has been suggested that primary prevention of GC could be achieved through a strategy of screening and treating H. pylori infection. (11)

In 2013, an IARC working group reviewed the evidence accumulated in support of mass H. pylori eradication as a strategy for preventing GC. Based on the favorable results of controlled clinical studies and observational studies, a group of experts confirmed that this strategy is effective. (19) For this reason, the IARC recommended that health care agencies include this strategy in national cancer control programs.

In January 2014, a global consensus was reached in Kyoto, Japan for evaluation of the management of chronic gastritis associated with H. pylori. Its conclusions establish that H. pylori eradication could prevent GC and that all carriers of H. pylori should be treated in order to eradicate this pathogen. (21) Elimination of H. pylori from the population could eliminate approximately 75% of GC. (22)

Our attention should be focused on how this strategy is carried out, for example, by identification of H. pylori patientss within the asymptomatic population and eradication before GC develops. However, the current strategy must depend on H. pylori infections and the incidence of GC within that population. (23)

A metaanalysis of three studies (Forman, Parsonnet and Nomura) found that people infected with H. pylori had a great risk of developing GC than did uninfected people with an OR of 3.8. Uemura has shown that patients untreated H. pylori infections had a greater chance of progression to GC in the next 12 years than did uninfected patients. (12)

Recent metaanalyses and studies with low statistical power indicate that the H. pylori eradication reduces the risk of GC developing by approximately 40% in primary prevention studies of asymptomatic individuals and by 54% as a tertiary prevention strategy against a second appearance of GC after endoscopic resection of early GC. It is not known if there is a cut-off time during the Correa cascade after which H. pylori eradication is no longer a deterrent to progression to GC. (12, 24)

A study by Lee et al. which included 24 publications (14 primary prevention studies and 10 tertiary prevention studies) with more than 48,000 individuals with follow-ups of 34,000 people/years has shown that the benefit of H. pylori eradication were more evident in areas where the incidence of GC is higher. However, risk reduction was evident in almost every individual evaluated in the study. Presumably, high-risk populations in low-risk countries, including immigrants who have been infected since childhood, benefit significantly from eradication. (12)

In another study, 544 patients who had undergone early GC endoscopic surgery were randomized to receive H. pylori eradication treatment. Metachronous GC was detected in nine patients in the group that received treatment and in twenty-four of the patients in the group that did not receive treatment, with $p < 0.01$. This indicates that the preventive effect of H. pylori eradication therapy in these patients significantly reduced the risk of metachronous GC. (25)

One intervention strategy in the carcinogenic phase of GC's natural history is the policy of diagnosing and treating H. pylori infections, especially before gastric atrophy and intestinal metaplasia occur. Nevertheless, patients with atrophy and metaplasia should also receive eradication therapy if bacterial infection is present even though there will be a time of no return after which therapy will have no justification because the mucosal damage will have already happened. (24)

Some researchers are trying to pinpoint the moment at which H. pylori generates changes in a person's deoxyribonucleic acid (DNA) and when that damage leads to irreversible development of cancer even if the infection is eradicated. (26) Determination of this point of no return will help define when eradicating the infection can guarantee the recovery of mucosal damage, stop the process and prevent the development of cancer.

A large number of medical professionals in Colombia do not have a clear, deep understandings of what gastritis implies in terms of risk, natural history, intervention and follow-up when faced with a pathology report of chronic atrophic gastritis with or without intestinal metaplasia. (14)

The incidence of GC increases with age, and the impact of H. pylori eradication on the incidence of GC depends on the population studied. (23)

Evidence suggests that all individuals with H. pylori gastritis should be treated. In countries with high-risk populations for GC, this strategy is recommended for young people under 20 years of age given that the infection is acquired in childhood. This knowledge may have clinical utility for stratifying individuals with H. pylori infection into those who are at high risk and those who are at low risk for GC in order to create personalized follow-up schemes. (12)

The question of how to prevent GC is addressed in Figure 2. The results support a strategy of eradicating the bacteria in countries where H. pylori and GC are common. Then, the current strategy should be carried out depending on the prevalence of H. pylori and GC. (23) The participants in the 2014 Kyoto consensus unanimously recommended implementation of H. pylori eradication therapy before precancerous changes develop. (21) The reason is the risk of progression to gastric atrophy and to intestinal metaplasia would be reduced along with the later risk of GC.

This strategy of screening for and treating H. pylori infections seems to be the best approach for reducing cancer risk. However, the implementation of this strategy at the population level requires a systematic approach. The program must also be integrated into national health care priorities so that limited resources are effectively allocated and used. Implementation may require adoption of an appropriate strategy. Within the population there are subgroups that vary in risk, so that it is impossible for the approach to be the same for everyone. (11)

Treating all patients with infections documented by histology or rapid urease test would not be justified because it would not be cost-effective. It is necessary to define a high-risk group within that population.

High Risk Group

High risk individuals might be defined as those from high-risk areas, especially in populations with an incidence greater than 20/100,000 inhabitants, who have a first degree family member with a history of GC, and who have histories of heavy smoking, and heavy salt and alcohol consumption (Figure 3). (24, 27)

Cost Analysis

The literature shows that diagnostic and treatment programs for H. pylori patients are more cost-effective in countries where the incidence of GC is higher than in low incidence countries. (30, 31) Two studies have shown that the optimal screening age is between 20 and 30 years because screening in older cohorts was less cost-effective. (32)

H. pylori screening is cost-effective because of the relatively low cost of H. pylori testing and treatment and the fact that screening is done only once. The estimated costs for detection and treatment of H. pylori are less than 1% of the costs of GC treatment in all studies. This means that the strategy of diagnosing and treating H. pylori entails considerable cost savings. GC consensus recommends blood test screening. In high prevalence populations, blood tests are used more frequently than the breath test while in low prevalence populations, the fecal antigen test is used more than the other two options. It should be taken into account that acceptability of the test is one of the requirements for introduction of this strategy in a study population. It has been found that blood tests and fecal antigen tests are more cost-effective than the breath test. Repeating screening and/or treatment and limiting treatment to those with CagA strains do not appear to be cost-effective policies. (32)

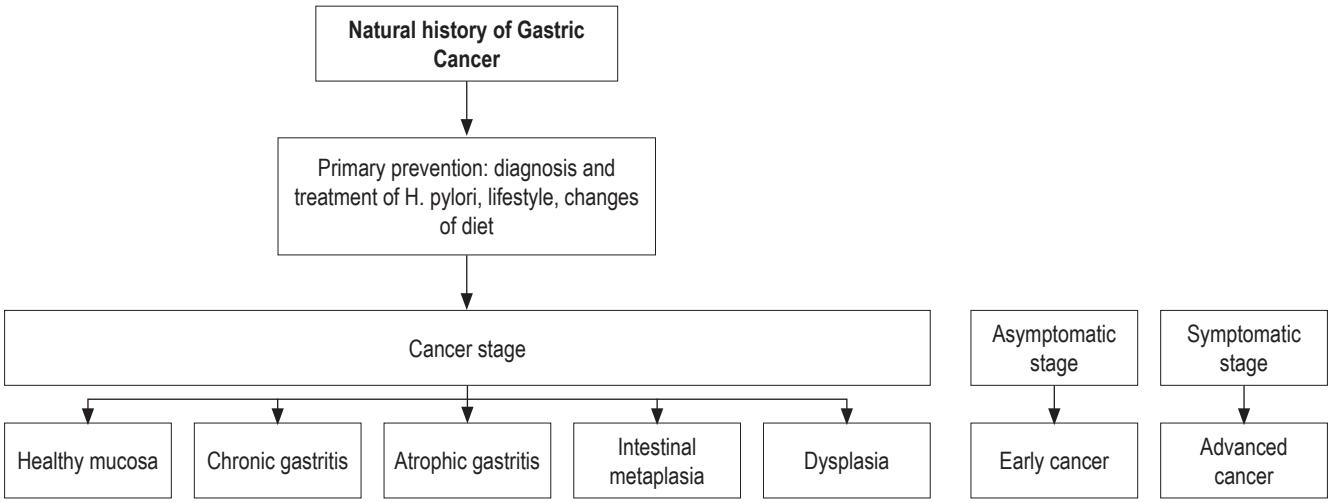

Figure 2. Primary GC prevention strategies. Taken from: Lee YC et al. Gut Liver 2016; 10 (1): 12-26.

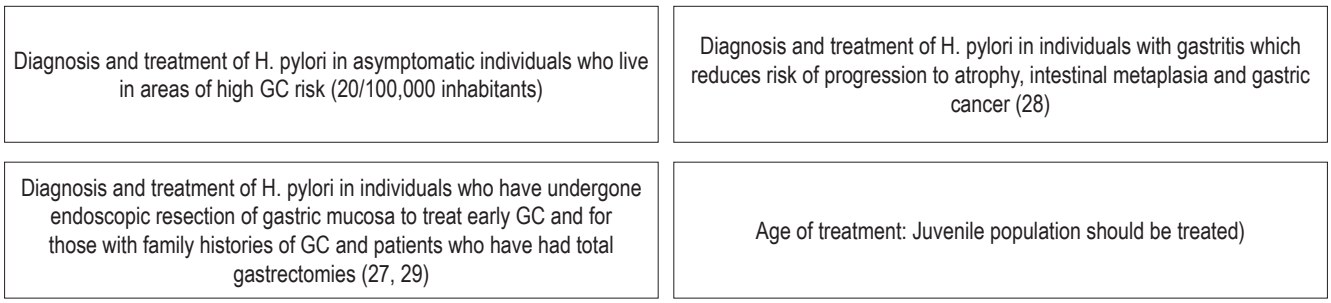

Figure 3. Summary of primary prevention strategies.

A large-scale study for the prevention of colon cancer and gastric cancer through the detection of fecal occult blood and fecal antigen for H. pylori is being carried out in Taiwan. Patients infected with H. pylori receive treatment. The results of this study are not yet known. (11)

Gastric Atrophy

Because GC develops over a long period of years to decades, the frequency of gastric atrophy is very low before the age of 40 (<5%). Only 5.9% of GC patients are younger than 40. (33, 34)

A study by Pelayo Correa in an area of high GC incidence reported that, in individuals over 40 years of age, the prevalence of chronic atrophic gastritis was 57%, the prevalence of intestinal metaplasia was 38%, and the prevalence of dysplasia was 10%. (35) This means that development of precancerous lesions and then identification of lesions can also take several years. Therefore, endoscopic follow-up of high risk patients can help identify malignant lesions early when they are still operable and there is a high probability of curing the patient. A 10-year follow-up study has reported that the figures for progression to GC for patients with atrophic gastritis, intestinal metaplasia, mild dysplasia and severe dysplasia are 0.8%, 1.8%, 4% and 33%, respectively. (36)

Patients with atrophy or extensive intestinal metaplasia should be followed up with endoscopy every three years. Patients with moderate atrophy or intestinal metaplasia limited only to the antrum do not need follow-up. (37) Management should be individualized according to other factors such as family history of GC, geographic origin, smoking and salt consumption.

Dysplasia is a high risk indicator for GC and should be confirmed and classified by two pathologists due to interobserver variability.

European guidelines recommend that patients with extensive atrophic gastritis or extensive intestinal metaplasia should have endoscopic follow-ups every 3 years. The incidence of GC in 10 years of follow-up for patients with atrophic gastritis is 0.8%. For patients with intestinal metaplasia, it is 1.8%, so the endoscopic follow-up of these 2 groups should be different. (37)

The operative link for gastritis assessment (OLGA) was established to evaluate the degree and location of atrophy. During diagnosis and follow-up of premalignant lesions, it is recommended that at least 5 samples be taken from patients undergoing endoscopy. Samples should include two from the antrum, two from the corpus, and one from the incisure. A biopsy sample from the incisure is needed because the prevalence of intestinal metaplasia is higher at this site than at any other location in the stomach. Intestinal metaplasia usually begins in the incisure and spreads to the antrum and the corpus. (37, 38)

Intestinal Metaplasia

Intestinal metaplasia is classified as either complete or incomplete. Whether intestinal metaplasia is reversible is a matter of controversy which is the reason a point of no return is under investigation. (39, 40) Complete intestinal metaplasia is considered a short-term reactive process that usually regresses while incomplete intestinal metaplasia is related to chronic prolonged damage, so it is more likely to progress to dysplasia. (41)

Patients with intestinal metaplasia may have up to 10 times more risk of GC than the general population. (42) There is controversy about the usefulness of classifying intestinal metaplasia in clinical practice. Incomplete intestinal metaplasia significantly increases the risk of GC beyond that of complete intestinal metaplasia. (2, 42, 37, 39)

Prevention and treatment of gastric atrophy and intestinal metaplasia decrease the prevalence of GC. H. pylori eradication is the fundamental management step while detection of GC in its early stages is the other strategy for these patients. (40)

Correa proposed an algorithm for managing and monitoring preneoplastic lesions. For patients with intestinal metaplasia, the presence of H. pylori and the extent of intestinal metaplasia should be measured. If the infection is present, it should be treated. If intestinal metaplasia is extensive

and incomplete, digestive endoscopy should be repeated every year and then every three years if the lesion persists. Otherwise monitoring is not required. (43) Patients with intestinal metaplasia who have at least one of these risk factors - incomplete intestinal metaplasia, family history, history of smoking, and salt consumption - may have a higher risk of developing GC and would probably benefit from more intense and frequent endoscopic monitoring. (33, 37)

Digestive endoscopy's diagnostic performance has been poor in the West, so the diagnosis of gastric atrophy and intestinal metaplasia requires systematic biopsies of the corpus and the antrum. (44) The protocol for staging with the OLGA system includes 5 biopsies: two from the antrum, two from the corpus, and one from the incisure. A greater number of biopsies may increase sensitivity. (37-39)

In a case-control study, the OLGA protocol identified 61.8% more cases of atrophy than did protocols with fewer biopsies. This could allow correction of the under diagnosis of gastric atrophy. (45)

It would be justified to practice quality digestive endoscopy to search for premalignant lesions in the high-risk population from the age of 40. Their extent and the risk of GC according to the OLGA system would determine the frequency of endoscopic follow-up. (7, 33, 39)

Intestinal metaplasia is a premalignant condition that can result from a process of adaption to an environmental stimulus such as H. pylori infection, smoking and/or high levels of salt consumption. (40) English studies that evaluated benefits of follow-ups for patients with intestinal metaplasia have found the incidence of GC to be 11%. Endoscopic follow-up was associated with earlier detection of GC and improved survival. (40)

Cancer detection figures range from 33% to 85% in European studies of endoscopic follow-up of patients with intestinal metaplasia, dysplasia. (40)

In the low-risk populations of the United States, the risk of progression is low and clinical follow-up is not indicated unless there are other risk factors for GC such as family history or Asian or Latin American country of origin. (42)

A European consensus suggests that endoscopic follow-up should be performed with mapping and biopsies within one year of detection of low-grade dysplasia in a patient with intestinal metaplasia. The ideal frequency of endoscopic monitoring is not known. Follow-ups may be suspended when two consecutive endoscopies are negative for dysplasia. Unlike patients with low grade dysplasia, patients with high grade dysplasia should undergo surgical or endoscopic resection due to the high probability of coexisting invasive adenocarcinoma. Twenty-five percent of patients with high grade dysplasia can progress to adenocarcinoma within one year. If H. pylori infection is identified, it must be eradicated even though controversy remains as to whether empirical eradication should be performed when intestinal metaplasia is diagnosed. (42)

The presence of incomplete intestinal metaplasia is a recognized predictor of increased risk for development of high grade dysplasia or GC in areas with high prevalence such as Japan. Several studies have concluded that incomplete intestinal metaplasia identifies patients at high risk of developing GC, and they require intensive follow-up (Figure 4). (46)

Dysplasia

Gastric dysplasia is a precancerous lesion and is the penultimate stage in the cascade of gastric oncogenesis, as formulated by Correa. Therefore, identification, management and monitoring of this lesion is important for early detection and prevention of GC. Dysplasia is usually classified as low or high grade. (47)

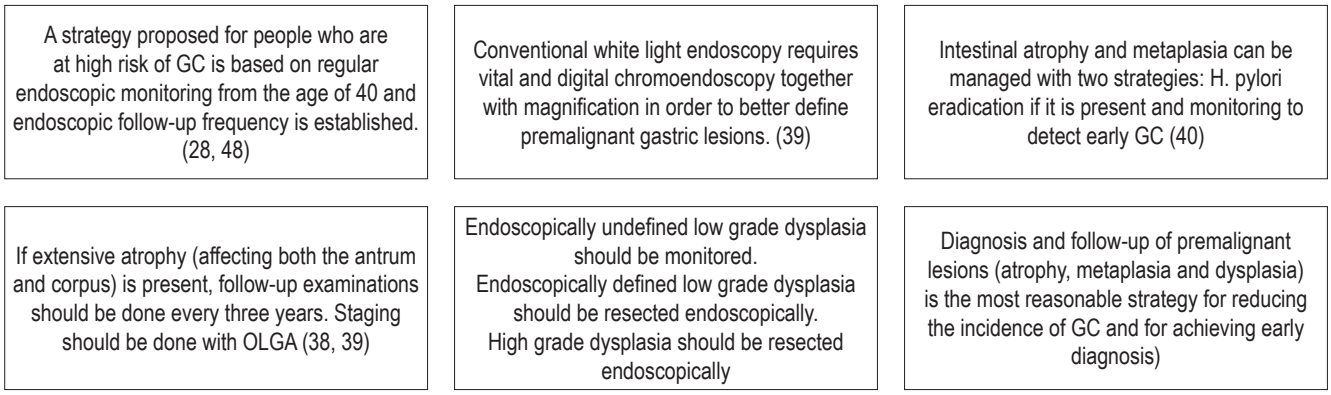

Figure 4. Summary of secondary prevention strategies.

Patients with dysplasia are generally men and who are 10 years younger than their relatives with GC (61.35 years for dysplasia and 70 years for GC). (47)

Dysplasia can be found anywhere in the stomach, but most often it is found in the antrum. Dysplasia is most often discovered incidentally during screening endoscopies. (47)

The real risk of progression of dysplasia to carcinoma is unclear because it is difficult to establish the natural history of dysplasia. However, several studies have shown that high-grade dysplasia has a high risk of progressing to either carcinoma or synchronous carcinoma. Figures ranging from 60% to 85% have been reported in an interval of 4 to 48 months. It is also known that 25% of patients with high-grade dysplasia have progressed to carcinoma within one year of diagnosis. (39, 47)

High-grade lesions require endoscopic resection due to their potential for progression to carcinoma and coexistence with carcinoma. When lesions are not well defined endoscopically, it is recommended that they be followed up one year after diagnosis. Lesions with high grade dysplasia should be managed with endoscopic resection. (47)

Sometimes endoscopic resection is indicated not only for diagnosis but for treatment of dysplasia.

Asymptomatic (Screening) Phase

The asymptomatic period is when cancer can be detected through screening tests before the typical symptoms needed for diagnosis appear. This phase is defined as the time from the onset of cancer to the onset of symptoms. It is the ideal time for screening programs. (11)

This period is a theoretical concept that is currently impossible to measure in particular cases even though it is the statistically most important parameter for defining the screening interval in the general population. (11) This time has been defined for GC as 2.37 years on average. This is the reason the Koreans recommend screening every 2 years. (11) Nevertheless, this average changes with age: in 40 to 49 year old population, it is 1.25 years; from 50 to 59 years old, it is 3.18 years; and from 60 to 69 years old, it is 3.74 years. This may explain why endoscopic screening in high-risk groups should include follow-ups annually or every 2 years. (11)

When cancer is diagnosed by screening, healing may be possible. and patients may survive for long periods of time. However, this phase of GC is relatively short. Prostate cancer, which has a long asymptomatic phase, can be diagnosed early and asymptomatically through screening by testing for prostate specific antigen (PSA). (11)

On the other hand, early GC progresses to advanced GC in 33 to 48 months, and it may be asymptomatic part of this time (Figure 5). (49)

Symptomatic Phase

The initial stage of GC is practically asymptomatic, and symptoms appear when the disease is very advanced,. At that point, curative surgical treatment is often impossible. In this phase, only 10% of GC patients survive. (50)

The risk of developing GC increases with age. GC occurs most frequently between 50 and 80 years of age. GC in people under 30 is rare. (6)

Out of a total of 600 patients in the REGATA study, 5.9% were under 40 years old, 10.1% were between 40 and 49 years old, 18.9% were between 50 and 59 years. and 65.1% were older than 60 years. GC is twice as frequent in men as in women. In this same study, 65% were men and 35% women. (34)

In 2008, Adrada et al. published a series of GC patients in which 92.4% had advanced lesions. (51). Martínez et al. found that 97% of patients had advanced tumors. (52)

Another important issue is the cost of handling patients with advanced lesions. Gaviria and Cubillos have established direct costs for diagnosis, staging, medical procedures and medical devices in caring for patients with advanced GC in Colombia. Costs are COP 12 million for stage II and COP 27 million for stage III. They established that the higher the stage, the higher the costs (Figure 6). (52)

CONCLUSIONS

GC is an ideal candidate for preventive strategies. However, while primary prevention is facilitated by the recognized objective of H. pylori, effective secondary prevention strategies have obstacles such as high costs and the need for significant human and technical resources.

More than a decade ago a mathematical model showed that screening for H. pylori infections followed by eradication could be cost-effective in countries with high incidence of GC and high GC mortality rates. It was also shown that the benefit was only significant in a subgroup of patients without precancerous lesions. A metaanalysis of 7 studies conducted in areas of high incidence of GC demonstrated a reduction in the risk of GC among patients who underwent H. pylori eradication (relative risk [RR]: 0.65). This primary prevention strategy is cost-effective in countries with high incidences of GC.

Eighty-four percent of GC patients are above 50 years of age, and of this group 65.1% are from 60 to 70 years old. Generally, patients with dysplasia are men and are 10 years younger than their relatives with GC (61.35 years for dysplasia and 70 years for GC), so the strategy for the average population should be 10 years earlier than the age group with the greatest prevalence. In other words, the endosco-

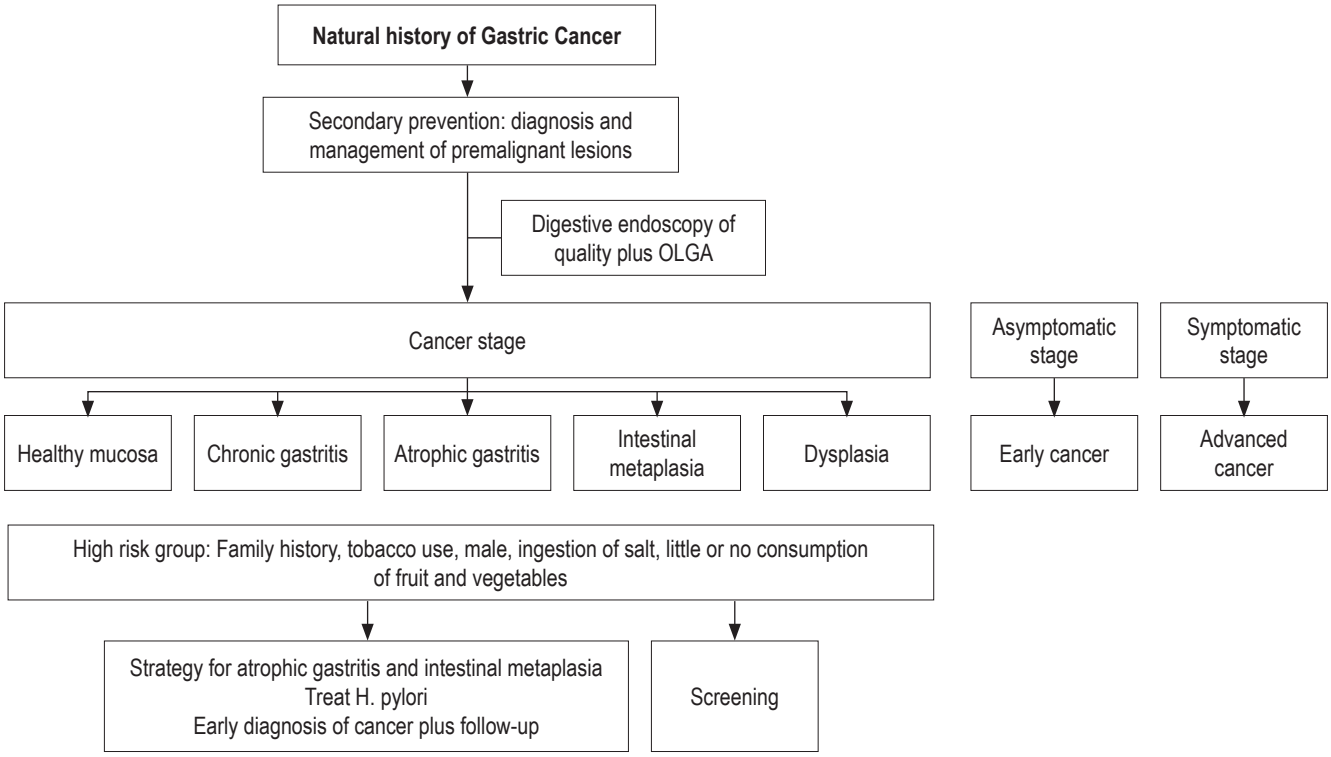

Figure 5. Secondary prevention strategies during the natural history of GC.

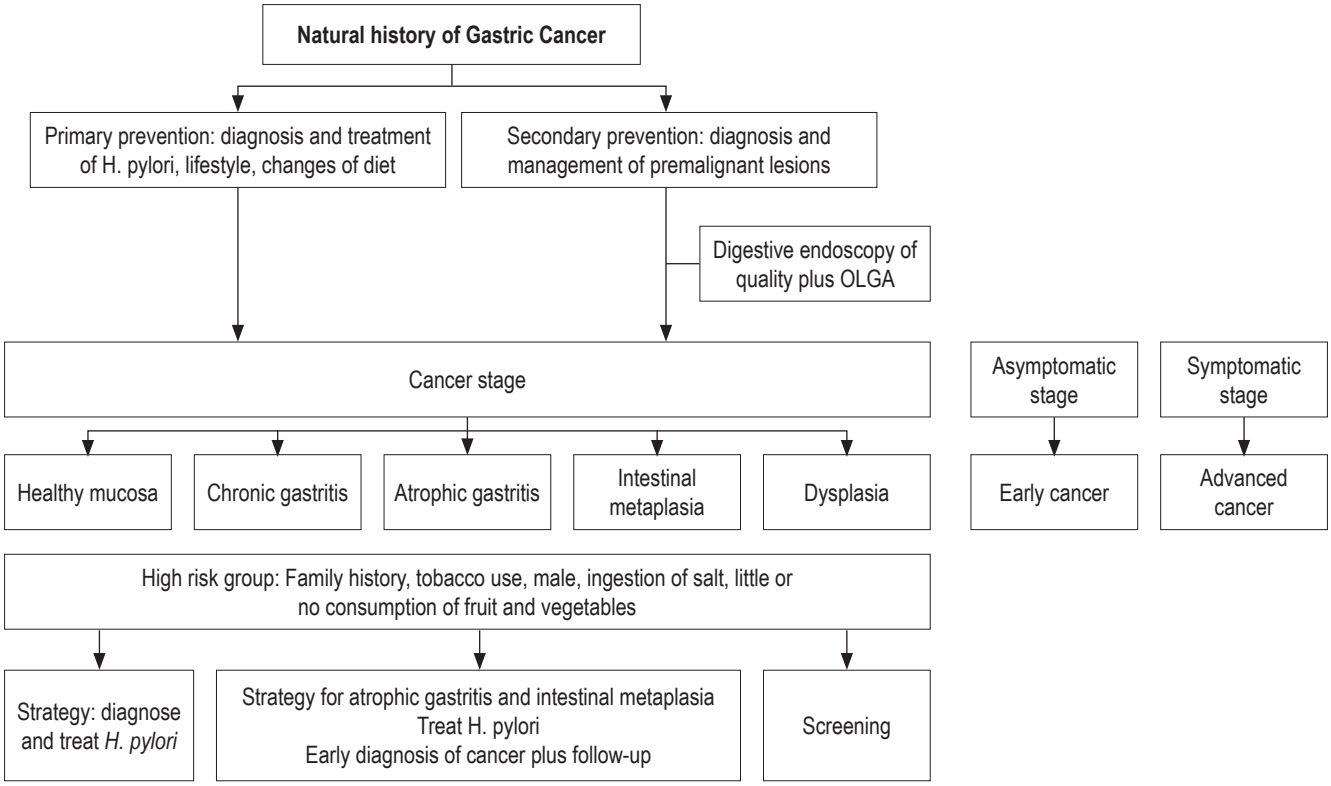

Figure 6. Summary of primary and secondary prevention strategies. Natural history of GC.

pic surveillance and risk stratification for those over 50 year should be initiated.

The current incidence of GC in any population is dependent on a number of variables including the proportion infected by H. pylori, the severity of gastric atrophy and the speed of atrophy's development.

It is necessary to change this disease's landscape by creating sensitivity to this public health problem within the medical association and at the level of those responsible for health care policies. It is also necessary to develop clinical practice guidelines aimed at preventing GC.

Primary and secondary prevention strategies that impact the natural history of GC should be established.

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Menetrier disease: Case report with video

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Abstract
Menetrier disease (also known as giant hypertrophic gastritis or hypoproteinemic hypertrophic gastropathy) is a rare entity characterized by protein losing enteropathy, hypochlorhydria and thickening of the mucosal folds of the fundus and the gastric corpus. Its constellation of classic symptoms includes nausea, vomiting, abdominal pain and peripheral edema, and it is associated with increased risk of gastric cancer. Nevertheless, its pathophysiology is not yet fully understood and clinical and endoscopic diagnosis can be difficult to establish. This article describes a clinical case and provides a brief review of the literature.

Keywords
Menetrier disease, mucosal hypertrophy, hypoalbuminemia.

INTRODUCTION

The French pathologist Pierre Menetrier (1859-1935) first described the disease that bears his name in the *Archives de Physiologie Normale et Pathologique* in 1888. Menetrier described seven individuals who exhibited two different macroscopic patterns of gastric hypertrophy: polypoid adenomas and sheet-like polyadenomas. He likened the patterns of the thickened gastric mucosa to cerebral convolutions. (1, 2) The Office of Rare Diseases of the National Institute of Health of the United States of America considers Menetrier disease to be rare, which means that its prevalence is less than 1 in 200,000 individuals. It is sometimes known by other names, including giant hypertrophic gastritis and hypoproteinemic hypertrophic gastropathy. (2) Since there are no pathognomonic characteristics for diagnosing Menetrier's disease, diagnosis is based on clinical and pathological characteristics. This, together with its rarity, poses a diagnostic and therapeutic challenge.

CLINICAL CASE

The patient was a 19-year-old man who began to suffer from abdominal pain and distention at 12 years of age during late childhood and early adolescence. His weight and height were both low for his age. He had been treated by different specialties until 2016 when he came to our service for upper digestive tract endoscopy as part of an evaluation requested by the attending physician. Thick gastric folds were found in the fundus and corpus with clearly decreasing distensibility (Video 1). From the clinical point of view, asthenia and dyspepsia were the predominant symptoms. During physical examination the patient was pale and had edema grade II in his lower limbs.

Paraclinical tests including a complete blood count, albumin, nitrogen and urine analysis were requested. The patient was found to have normocytic, normochromic, heterogeneous anemia. His hemoglobin level was 11.2 g/dL, his serum albumin level was 2.8 g/dL, and his creati-

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Video 1. Endocopy of Ménétrier's disease. Thickened proximal gastric folds affected by edema can be seen. https://youtu.be/sQNxWFhjeq0

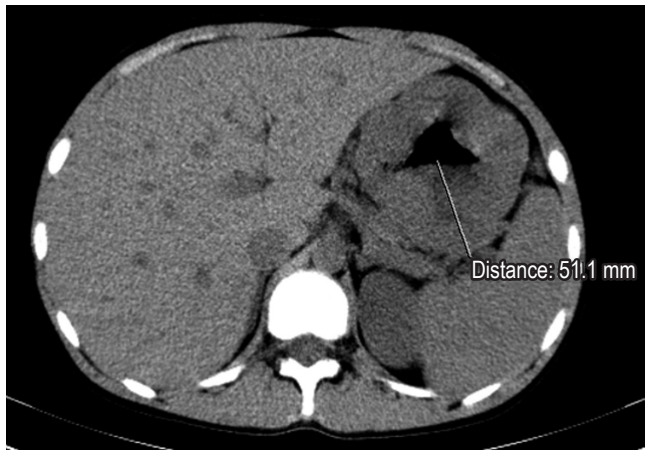

Figure 1. Image of patient's CT scan.

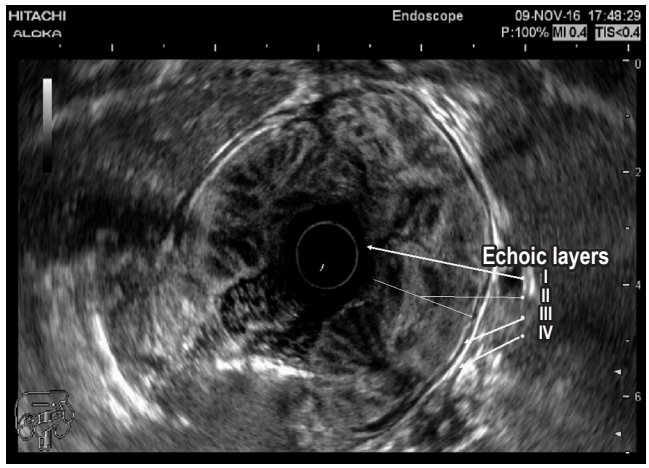

Figure 2. Image of the patient's gastric EUS

nine level was 0.8 mg/dL (normal). The urine analysis did not find proteinuria. Given the clinical, paraclinical and endoscopic findings, computed tomography (CT) of the abdomen was performed. It found thickened gastric walls with diffuse, marked and symmetric gastric folds without evidence of nodular lesions. The maximum thickness was 53 mm (Figure 1). Findings from gastric endoscopic ultrasonography (EUS) were similar to those described of the upper digestive tract endoscopy, but thickening of the gastric wall dependent on the first and second echoic layers (mucosa and muscular mucosa, respectively) was found. Anechoic spaces were found in the second echoic layer respecting the third and fourth echoic layers (submucosa and muscularis propria, respectively) (Figure 2).

The histology report from biopsies taken in the upper digestive endoscopy showed hyperplastic gastritis with "Menetrier's disease pattern, and the patient was negative for Helicobacter pylori (Operative Link on Gastritis Assessment [OLGA]: 0). A follow-up in July 2017 found the patient's symptoms due of abdominal pain and distention were worsening and that there was associated vomiting, nausea and anasarca. Surgical management was decided upon.

DISCUSSION

Menetrier's disease is most often found in men between the ages of 30 and 60 years although cases have also been reported in childhood. Clinically, patients present abdominal pain, nausea, vomiting and edema of the peripheral tissues (imbalance of osmotic pressure due to the selective filtration of proteins through the gastric mucosa). (3). This disease tends to be progressive, although its pathophysiology is still unknown. Transgenic mice models overexpress transforming growth factor alpha (TGF-α) in the stomach and undergo changes that resemble those found in Menetrier's disease. In addition, the receptor for epidermal growth factor (EGF) in foveolar mucus cells is overstimulated by TGF-α, its ligand, which causes excess mucus secretion and malabsorption of nutrients.

From the clinical point of view, onset is usually insidious and progressively includes characteristics that are associated with increased risks of gastric cancer. Although the magnitude of this risk is not entirely clear, various authors place it between 0% and 10%. (3, 4) Variants with abrupt onsets have also been described. These have been reported most frequently in relation to spontaneous remission related to treatment of associated cytomegalovirus (CMV) infection or H. pylori infections. Some authors have also described associations with autoimmune diseases such as inflammatory bowel disease, sclerosing cholangitis and ankylosing spondylitis which suggests that there is an immunological component which has not yet been fully elucidated. (2, 5)

Endoscopically, the folds of the gastric mucosa are markedly thick especially in the fundus and the corpus rather than in the antrum. Gastric pH is high due to the loss of parietal cells, and there is copious production of thick mucus secondary to foveolar hyperplasia that occurs most commonly in the mucosa. This causes mucosal thickness to increase by one cm or more (in our clinical case it reached 5 cm). This is a necessary condition for diagnosis. (5)

Histological alterations include reduced numbers of parietal cells and main cells and atrophied oxyntic glands. Deep glands may be cystically dilated and predominantly chronic inflammatory cells with dispersed eosinophils infiltrate the lamina propria in variable amounts. Smooth muscle hyperplasia and edema are associated with decreased numbers of fundic glands which are replaced by mucous glands (pseudopyloric metaplasia). This totally abnormal mucosal architecture generates loss of protein which is frequently increased by superficial ulcers. (4-6)

Differential diagnosis revolves around other entities that thicken gastric folds. These include lymphocytic gastritis, polyposis syndromes, hyperplastic polyps, plastic lymphadenitis and lymphoma (Table 1). EUS is a useful tool for differential diagnosis since it can exclude a thickening of vascular origin in cases where biopsies may cause significant bleeding. Consequently, it is recommended that EUS precede any decision to take biopsies in cases of thickening of gastric folds. Thickening originating in the second echoic layer supports a diagnosis of Menetrier's disease (Figure 2). (6, 7)

Treatment is usually surgical, and partial or total gastrectomy is currently considered the treatment of choice. Nevertheless, several drug therapies have been proposed. They include weekly administration of cetuximab which has improved patients' quality of life. Despite this, some patients followed up for 40 months required long-term gastrectomy, so the use of cetuximab has only been recommended as the first line for management of Menetrier's disease in cases of relapses after gastrectomies. (6) Other drugs including famotidine and cimetidine have shown favorable results including reports of decreased symptoms. In the case of cimetidine, decreased protein loss has also been reported. Steroids and antibiotics have also been used but with conflicting results. It should be noted that, given the low prevalence of this disease, none of these treatments have had clinical trials with the required methodological rigor, so all reports are now considered anecdotal experiences. (8)

CONCLUSION

Menetrier's disease is recognized as a rare disease, so its diagnosis is difficult. Nevertheless, it is of crucial impor-

Table 1. Differential Diagnosis

Diagnosis	Distribution	Location in the stomach	Hyperplastic mucosa	Pathological findings
Menetrier's Disease	Diffuse	Fundus and Corpus, antrum relatively well-preserved	Foveolar epithelium	Massive foveolar hyperplasia
Hypertrophic lymphocytic gastritis	Diffuse	Fundus and Corpus, antrum relatively well-preserved	Foveolar epithelium	Large numbers of intraepithelial lymphocytes
Hypertrophic hypersecretory gastritis	Diffuse	Fundus and Corpus, Atrophied antrum	All layers	Hyperplasia of all glandular compartments
Zollinger-Ellison syndrome	Diffuse	Fundus and Corpus	Parietal cells	Parietal cell hyperplasia
Hyperplastic polyps	Focal	Fundus, Corpus, and/or antrum	Foveolar epithelium	Foveolar hyperplasia with distortion of architecture
Hamartomatous Polyposis Syndromes	Variable	Fundus, corpus, and antrum	Foveolar epithelium	Similar to hyperplastic polyps
Gastric adenocarcinoma and proximal polyposis	Variable	Fundus and Corpus	Oxyntic glands	Fundic gland polyps with high and/or low grade dysplasia
Diffuse gastric cancer	Variable	Fundus, corpus, and antrum	Not applicable	Diffuse infiltrating cancer
Lymphoma	Variable	Fundus, corpus, and antrum	Not applicable	Obliteration of gastric mucosa with infiltration of cells by lymphoma
Amyloidosis	Variable	Fundus, corpus, and antrum	Not applicable	Acellular, amorphous with eosinophilic material surrounding glands and vessels

Taken from: Silva PH et al. Rev Assoc Med Bras (1992). 2016; 62 (6): 485-9.

tance given the risk of associated malignancy. Based on available evidence, the currently recommended treatment is predominantly surgical, although there are other treatments that can be implemented in specific clinical situations such as relapse.

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The skin as a mirror of the gastrointestinal tract

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Abstract
We present four cases of digestive bleeding whose skin manifestations guided diagnosis prior to endoscopy. These cases demonstrate the importance of a good physical examination of all patients rather than just focusing on laboratory tests.

Keywords
Skin, bleeding, endoscopy, pemphigus.

Despite great technological advances in diagnosis of diseases, physical examination, particularly an appropriate skin examination, continues to play a leading role in the detection of gastrointestinal pathologies. The skin, the largest organ of the human body, has an area of 2 m^2 and a thickness that varies between 0.5 mm (on the eyelids) to 4 mm (on the heel). It weighs approximately 5 kg. (1) Many skin manifestations may indicate systemic diseases.

On the other hand, upper gastrointestinal bleeding, the most frequent emergency in gastroenterology, has a mortality rate between 5% and 14% and an incidence rate that varies geographically. Forty percent are caused by peptic ulcers while 10% to 24% are caused by esophageal varices. Rare causes account for less than 1% of etiologies, are very difficult to diagnose, but with a good physical examination they can be suspected. (2, 3)

This paper presents four rare causes of digestive bleeding that compromised the esophagus, stomach, duodenum and jejunum and whose diagnoses were guided by dermatological manifestations.

CASE 1: VULGAR PEMPHIGUS

This 46-year-old female patient suffered an episode of hematemesis with expulsion of whitish membranes through her mouth during hospitalization. Upon physical examination, she was found to have multiple erosions and scaly plaques with vesicles that covered the entire body surface. After a baseline diagnosis of pemphigus vulgaris, endoscopy found that the epithelium of the esophageal sphincter was compatible with esophagitis dissecans superficialis (Figures 1A and 1B). (4)

CASE 2: OSLER–WEBER–RENDU (OWR) SYNDROME

This 62-year-old patient was admitted to the emergency department due to hematemesis and melena. The physical examination revealed multiple red to purple papules and telangiectasias on the patient's lips, tongue and face. OWR syndrome was suspected, and endoscopy found multiple angiodysplasias in the patient's stomach (Figures 1C and 1D). (5)

CASE 3: HENOCH–SCHÖNLEIN PURPURA (HSP),

This 28-year-old patient was admitted to the emergency department because of episodes of coffee ground emesis associated with arthralgia, myalgia, and purple lesions on the knees and buttocks. HSP was suspected. Endoscopy found severe edema, erythema and erosion with thickening and infiltration of the mucosa in the duodenum. The patient's platelet count was 90,000 and there was no bleeding. Immunohistochemical study of a biopsy sample confirmed infiltration by immunoglobulin A (IgA) (Figures 1E and 1F). (6)

CASE 4: TYPE 1 NEUROFIBROMATOSIS

This patient was a 29-year-old woman who was admitted to the emergency department because of coffee ground vomitus, melena and recurrent episodes of rectal hemorrhaging. Physical examination showed "cafe au lait" spots and multiple neurofibromas associated with scoliosis. Endoscopy and colonoscopy found no lesions due to manifest occult digestive bleeding. Since balloon enteroscopy was not available, intraoperative laparoscopic enteroscopy found multiple masses that measured 10 mm to 40 mm in the proximal and middle jejunum. They were resected, and histopathological study confirmed that they were plexiform neurofibromas. (Figure 1G and H). (7)

CONCLUSION

These cases show that, despite advances in technology, a good physical examination remains essential for evaluation of patients. Good physical examination can guide the physician in finding unsuspected diagnoses once a digestive endoscopy is performed.

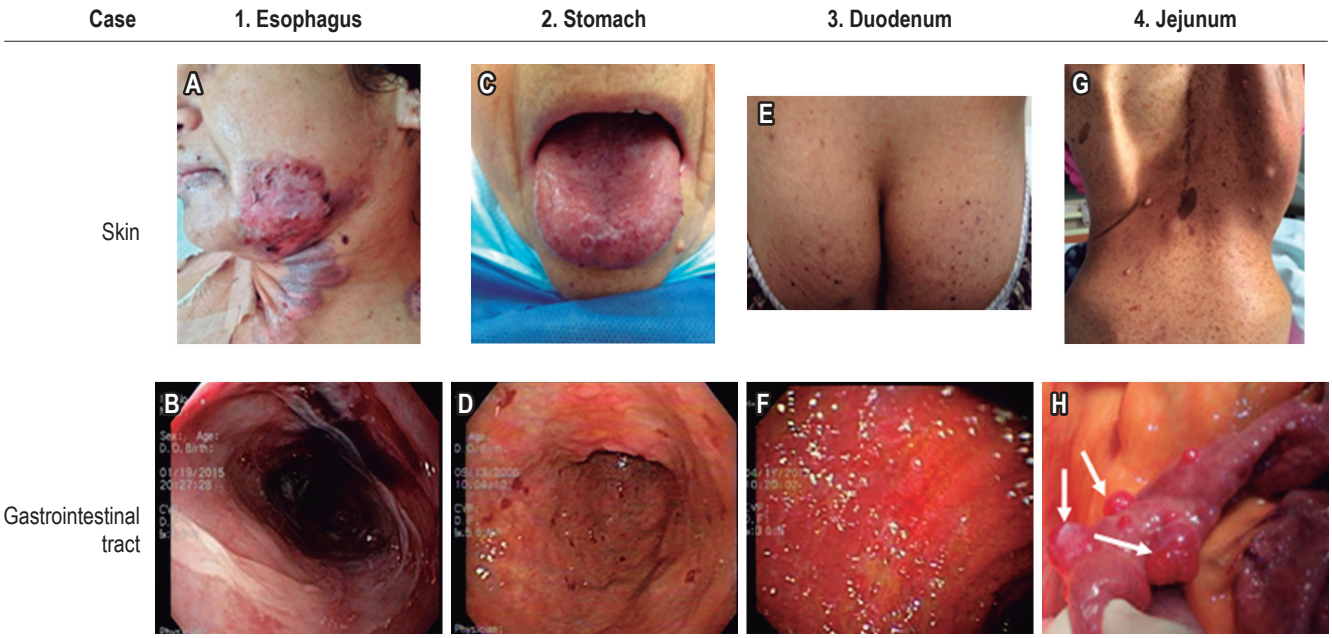

Figure 1. A. Pemphigus Vulgar. Erosions, crusty scabbing from bleeding and scaly plaques with vesicles can be seen in the labial commissure. Erosions, scabs and brownish macules with vesicles can be seen towards the periphery of these lesions in the mandibular region and neck. **B.** Esophagogastroduodenoscopy. The exposed submucosa can be seen in the proximal part of the esophagus, and the completely scaled epithelium can be seen in the distal esophagus. Esophagitis dissecans superficialis was diagnosed. **C.** OWR syndrome. Multiple reddish-purplish papules and telangiectasias can be seen on the dorsal surface of the tongue. **D.** Esophagogastroduodenoscopy. Multiple angiodysplasias can be seen in the distal corpus. They were treated with argon plasma coagulation. **E.** HSP. Purple papules can be seen on the buttocks at different stages. Palpable purpura and post-inflammatory macules are resolving lesions. **F.** Esophagogastroduodenoscopy shows marked edema, thickening of the mucosa, erythema and erosions in the first portion of the duodenum secondary to infiltration by IgA which tested positive in immunohistochemistry of biopsies. **G.** Neurofibromatosis type 1. "Cafe au lait" spots, multiple freckles, papules and nodular neurofibromas can be seen. Scoliosis is also visible. **H.** Laparoscopic intraoperative enteroscopy finds and resects multiple neurofibromas (arrows) in the middle jejunum. They were resected in block, and a primary anastomosis was performed.

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Simultaneous appearance of early gastric cancer and GIST

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Abstract

We present the case of a 74-year-old male patient who was admitted with symptoms of upper digestive bleeding. Endoscopy of his upper digestive tract found an ulcerated lesion and a subepithelial lesion in his stomach. Complete studies including gastric endoscopic ultrasound showed a mucosal lesion infiltrating the submucosa which was suggestive of early gastric cancer as well as a subepithelial lesion on the muscle that was suggestive of a gastrointestinal stromal tumor (GIST). Staging showed no metastatic compromise, so surgery was performed, and histology subsequently confirmed the findings.

Keywords

Hematemesis, manes, gastric cancer, gastrointestinal stromal tumor, GIST, synchronous tumor, ki 67, surgery, endoscopic ultrasound, submucosal dissection, gastrectomy.

INTRODUCTION

Gastric cancer's (GC) prevalence and mortality rate are high all around the worldwide. In 2008, there were 988,000 new cases of GC in the world, representing the fourth most frequent cancer after lung cancer, breast cancer and colon and rectal cancer: 738,000 deaths occurred making GC the second leading cause of cancer death. (1) In Colombia, it is the first cause of cancer death in men and the third cause of cancer death in women. (1) Digestive endoscopy is the diagnostic method of choice for GC, (2) but endoscopic ultrasonography (EUS) is a complementary method of choice for determining the depth of early GC. (3) It has the ability to visualize digestive tract strata with proven histological correlations. (3) Early GC is located in the mucosa and submucosa and may or may not involve lymph nodes. (4) Early GC is treated endoscopically by mucosectomy or endoscopic dissection of the submucosa, depending on the tumor's size and morphological characteristics as determined by EUS. (5) Advanced GC invades beyond the submucosa and compromises regional and distant tissue. (5) Management includes surgery and chemotherapy and radiation therapy.

Gastrointestinal stromal tumors (GIST), with an incidence between 10 and 15 cases per million people, are the most common tumors of the gastrointestinal tract. (6) Although they are usually diagnosed incidentally from radiological or endoscopic studies, their most frequent clinical manifestation is gastrointestinal bleeding. (5) Their most frequent location is the stomach, (7) and histologically more than 95% of GIST are positive for the KIT protein (CD117). About 90% have a mutation either in the c-KIT gene or in the PDGFRA gene. (8) In endoscopy, it can be seen as a subepithelial lesion sometimes with a central

ulceration. (9) In EUS it is a hypoechogenic lesion that is homogeneous and dependent on the muscular layer. EUS can be used in a complementary way to guide performance of a biopsy for use in histological diagnosis. (10) Computed axial tomography (CAT) is the imaging method of choice for characterizing an abdominal mass since it evaluates local extension and distance which is important because GIST can metastasize especially to the liver, omentum and peritoneal cavity. (11)

Management of GC depends on its extension and size. The goal of surgical treatment is resection with free margins, but lymphadenectomy is not necessary in view of the fact that lymphatic involvement is rare. (11) Since forty to fifty percent of patients who undergo surgery may experience recurrences, (12) tyrosine kinase inhibitors appear to be an excellent alternative treatment. (13) Wedge resection is the surgical management of choice, (14) and laparoscopic techniques have fewer complications, shorter hospital stays and less bleeding than do open resection techniques. (15) The best way to treat lesions that are smaller than 2 cm is still not clear from the available evidence, so unless distance extension is documented, which is rare, management should be expectant. (16)

This article presents the interesting case of one patient with simultaneous presentation of both of the pathologies discussed above.

CLINICAL CASE

The 74-year-old patient was admitted after three days of hematemesis and melena. Upper digestive endoscopy found an elevated, 20 mm in diameter lesion with an ulcerated center in the middle of the corpus towards the anterior wall as well as a 60 mm subepithelial lesion in the antrum. The initial endoscopic diagnosis a type 0-IIa elevated gastric lesion and a type 0-IIc subepithelial lesion (GIST?) (Figure 1). Multiple biopsies of the lesions were taken.

Based on the endoscopic findings, it was decided to extend the study through gastric endoscopic ultrasonography. It showed an elevated 20 mm hypoechoic lesion in the corpus that infiltrated into the mucosa and partially into the submucosa. In the antrum, a 60 mm in diameter subepithelial lesion with cystic spaces inside was found in the muscularis propria (Figure 2). No perilesional or celiac trunk adenopathy was found, and a diagnosis of early GC and GIST in the fourth layer was made. The biopsy taken from the lesion in the gastric corpus confirmed that it was a moderately differentiated gastric adenocarcinoma. A contrasted abdominal CT scan showed no metastasis from the GIST.

Submucosal dissection of the adenocarcinoma and surgical resection of the GIST were planned, but the patient developed acute bleeding due to ulceration of the GIST, so a subtotal gastrectomy with resection of the two lesions was performed. The pathology of the surgical specimen showed a moderately differentiated adenocarcinoma which only extended to the superficial submucosa (Figure 3). There was also a 7 x 7 cm antral lesion for which immunohistochemistry was positive for c-kit (Figure 4), positive for CD 34 positive, negative for S100. The mitotic index and ki 67 were both less than 2% (Figure 5). All nodes were negative for metastasis. The patient is asymptomatic, and evolution has been very satisfactory to date (1 year of follow-up). Since this was a case of early GC was early and the GIST was low risk, there was no need for complementary treatment.

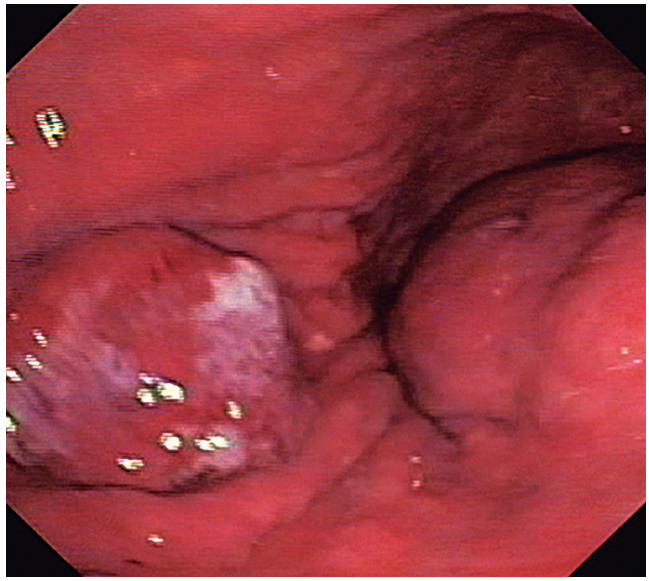

Figure 1. The image shows both lesions. The one on the left corresponds to early gastric cancer and the one on the right corresponds to GIST.

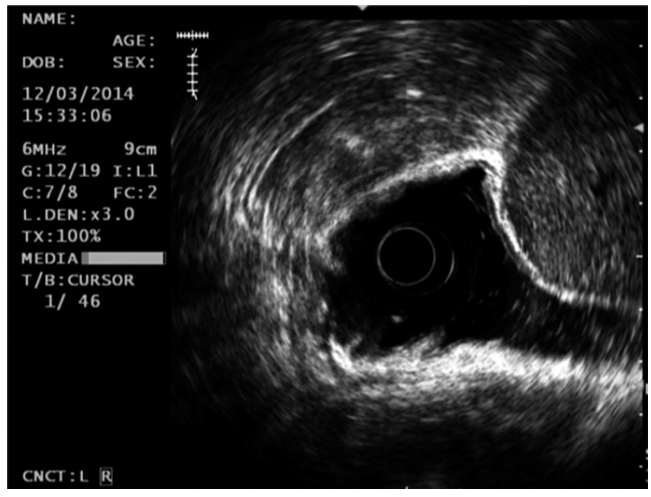

Figure 2. Gastric endoscopic ultrasound. GC on the left, subepithelial lesion on the right.

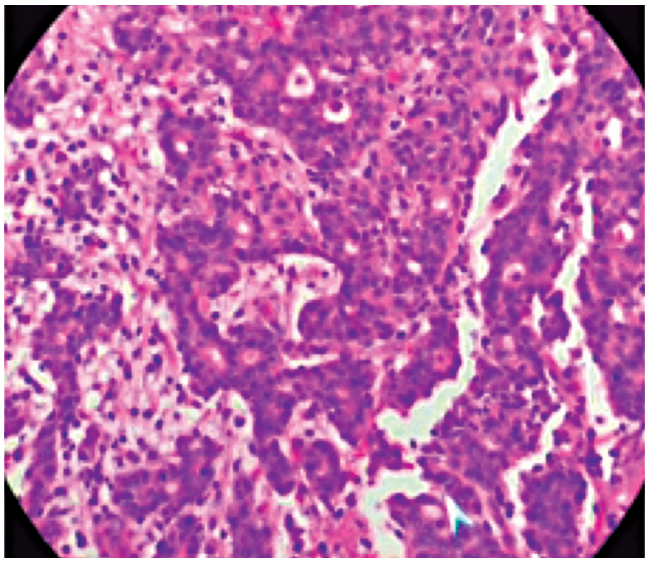

Figure 3. Moderately differentiated gastric adenocarcinoma.

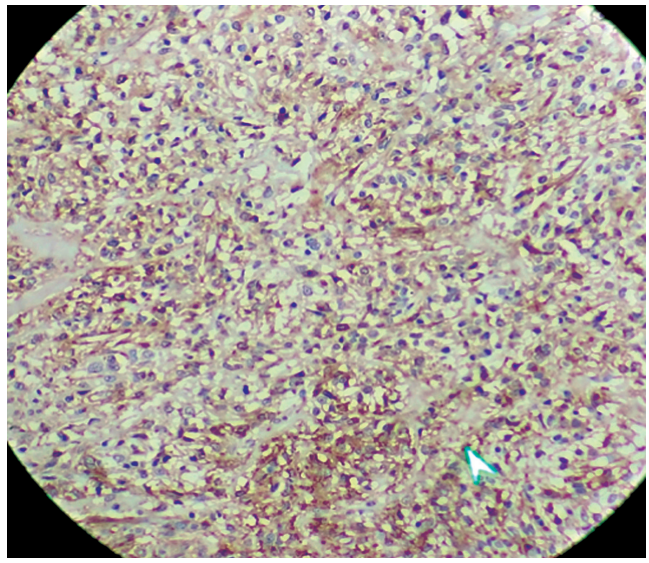

Figure 4. GIST positive for c-Kit.

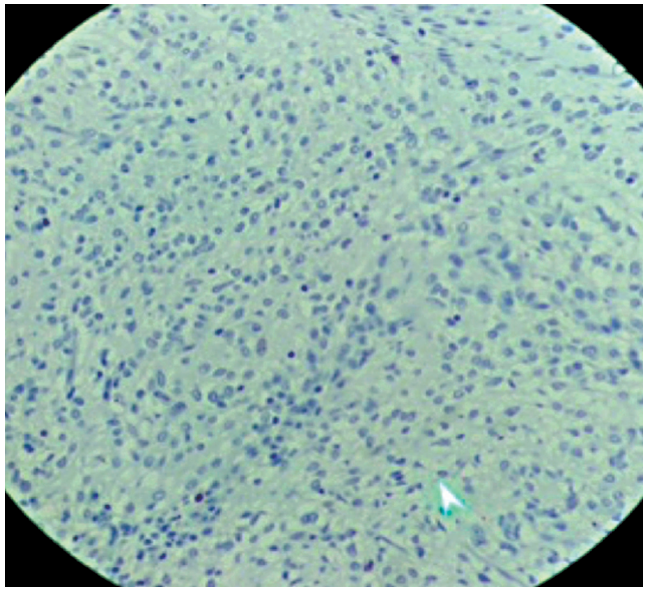

Figure 5. GIST positive for CD 34 but negative for S100.

DISCUSSION

GIST does not occur frequently with other malignancies although there are a few case reports and case series. A series of cases published by Krame et al. has demonstrated a higher frequency of other types of tumors in patients who either had GIST at the time of the study or had suffered from GIST earlier. (17) The study covered 836 GIST patients and found that 31.9% had other types of neoplasms. Of these 43.5% were gastrointestinal, 34.1% were urogenital or breast cancer, 7.3% were hematological, and 7.3% were skin cancer. Nevertheless, most of these were found up to 5 years after the diagnosis of GIST, and no synchronous neoplasms were described. Another series of 101 patients by Goncalves were found that 13.8% had other types of tumors. Of these, 57.1% (8 cases) had GC, but none of them were synchronous. (18)

Although a relationship between GIST and other neoplasms is already known, synchronous presentations have only been found in a very few case series. Wronski et al. published 28 cases of GIST with synchronous tumors and found that 57% of these were GC. (19) It is important to clarify that the type of studies that describe a relationship between GIST and GC cannot ascribe a causal association much less determine that one or the other pathology is a risk factor for the other.

Similarly, none of hypotheses about the occurrence of synchronous neoplasms with GIST have been proven yet. Larger follow-up studies and studies with larger sample sizes with comparisons with controls would be useful because they could establish whether there is a risk association between these pathologies. Nevertheless, reports like this illustrate possible association and thus refine the search for early GC in patients with GIST and vice versa.

In addition, the available evidence and its forcefulness require consideration of endoscopic management as the first-choice management for GC. The most effective type of endoscopic management is dissection of the submucosa. (5) On the other hand, laparoscopic wedge resection is the most appropriate choice for surgical management of gastric GISTs because it is high effective and has lower rate of adverse events. (16) In the case of this patient, the decision

taken to perform subtotal gastrectomy was mostly guided by the development of severe bleeding.

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DOI: http://dx.doi.org/10.22516/25007440.224 Case report

Perforation of the jejunum due to diverticular disease: A condition to consider in the elderly

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Abstract

Diverticular disease is the most common bowel disease after the age of 40 years. It is the most common finding in elective endoscopic procedures, and it has great relevance because of its broad manifestations which lead to frequent emergency service consultations. On the other hand, the prevalence of diverticulosis of the small intestine ranges from 2% to 5%. Clinical presentations such as bleeding, obstructions, abdominal pain, perforations, formation of abscesses and fistulas are usually more florid when they affect the colon. We present the case of an elderly emergency room patient with acute abdomen secondary to generalized peritonitis due to intestinal perforation caused by diverticular disease of the jejunum.

Keywords

Elderly patients, geriatrics, intestine, diseases of the jejunum, diverticulum, delirium.

INTRODUCTION

Diverticula are saclike formations produced by protrusions of mucosa through the muscular wall of the intestine. Their prevalence is similar in men and women, (1) but it increases with age from less than 20% at 40 years to more than 63% in people over 70 years of age. (2) Diverticular disease mainly affects the colon, especially the sigmoid colon. (2) Diverticula are less common in the small intestine, but 80% of diverticulosis of the small intestine occurs in the jejunum, 15% occurs in the ileum and 5% affects both. (3) A series of autopsies has reported that between 1% and 4.5% of bodies examined had diverticular in the jejunum and ileum. (4, 5)

The etiology of jejunal diverticula is not clear, but motility alterations have been considered, (6) and some nutritional risk factors such as low-fiber diets and diets rich in refined sugars increase formation of diverticula in general. (7) Low fiber intake results in poorly hydrated feces which can alter intestinal transit time which translates into increased colonic pressure. This makes it difficult to evacuate intestinal contents and promotes the formation of diverticula. (7) Other risk factors that may increase frequency of occurrence include changes in microbiota, constipation, sedentary lifestyles, obesity, smoking and consumption of non-steroidal anti-inflammatory drugs (NSAIDs). (2)

Up to 75% of cases of diverticular disease are asymptomatic. The most frequent symptoms are abdominal pain, (8) lower gastrointestinal bleeding, inflammation, abscess formation, perforations, and obstructions. (5) Diagnosis in the small intestine the can be difficult because there are no pathognomonic characteristics or specific symptoms. (9)

Consequently, it is vitally important to know the forms of presentation of atypical diverticular disease in elderly patients because the timely diagnosis will have an impact on the patient's survival.

CASE DESCRIPTION

The patient was a 67-year-old man who came to the clinic following two days of stabbing abdominal pain of moderate intensity located in the hypogastrium. Onset was gradual, then pain radiated to the mesogastrium and the right iliac fossa. It was accompanied by abdominal distension, postprandial emesis, two episodes of diarrhea without mucus or blood, and unquantified fever. Patient had experienced fluctuation of consciousness, disorientation and zoomorphic visual hallucinations.

The only comorbid history was chronic arterial hypertension which had been controlled with an angiotensin-converting enzyme inhibitor (ACEI). He had no history of surgery, cognitive compromise, or mental illness and had been functional condition and able to perform basic activities of daily life prior to admitting himself to the hospital (Barthel scale: 100/100).

Physical and mental examination at admission showed the patient to be lethargic, and temporospatially disoriented with a fluctuating state of consciousness. He was unable to maintain fluent conversation and had irrelevant thinking and incoherent language. The patient's temperature was 38.8° C, he had tachycardia with a heart rate of 120 beats per minute, his respiratory rate was 24 breaths per minute, and he was hypotensive with blood pressure of 90/50 mm Hg) and capillary filling of 4 seconds. His abdomen was markedly distended without peristalsis, with pain on superficial palpation on the flank and right iliac fossa. He exhibited central tympanism and voluntary abdominal defense.

The initial clinical diagnostic impression was sepsis of abdominal origin secondary to acute appendicitis accompanied by hypoactive delirium. This was based on a quick Sequential Organ Failure Assessment (qSOFA) score of three points plus the obvious psychiatric manifestations at the time which were correlated with a Short Confusion Assessment Method (Short-CAM) evaluation of acute onset and fluctuating course of mental state.

Intravenous fluids were administered and hemodynamic normality was achieved. Ampicillin and sulbactam were also administered and paraclinical studies were requested that. They showed a leukocyte count of 15,530/µL, a hemoglobin count of 10.4 g/dL, a platelet count of 130,000/µL, a C-reactive protein (CRP) level of 114 mg/dL, arterial gases with pH of 7.31, partial carbon dioxide pressure (pCO2) of 22.7 mm Hg, partial oxygen pressure (PO2) of 70.3 mm Hg, a bicarbonate (HCO3) level of 11.2 mmol/L and base excess (BE) of -12.7 mmol/L. Standing chest x-rays (Figure 1) and simple abdominal x-rays (Figure 2) were taken.

With these findings, an emergency exploratory laparotomy was performed. It found four quadrant peritonitis, a 10 cm segment of the jejunum with a congestive, edema-

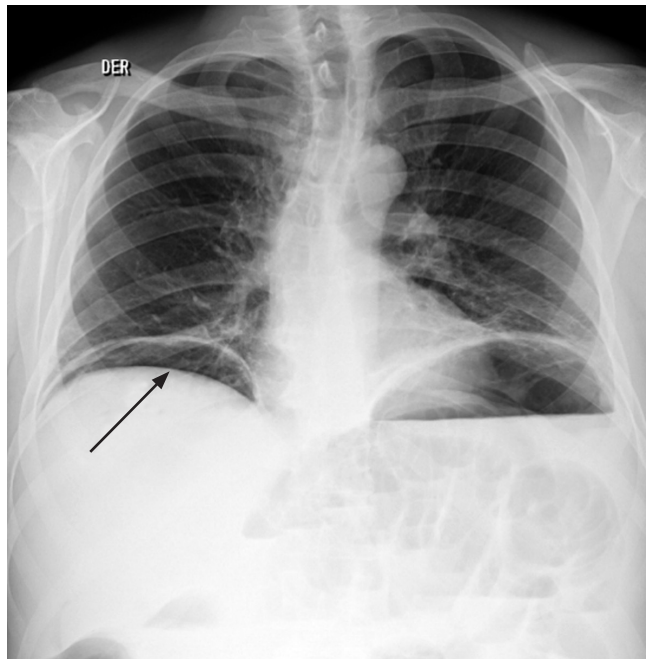

Figure 1. Posteroanterior standing chest x-ray shows bilateral pneumoperitoneum (arrow) with a bilateral basal subpulmonary collection of liquid on the left accompanied by the elevation of both hemidiaphragms and bilateral biliary reticular interstitial opacities without pleural effusion.

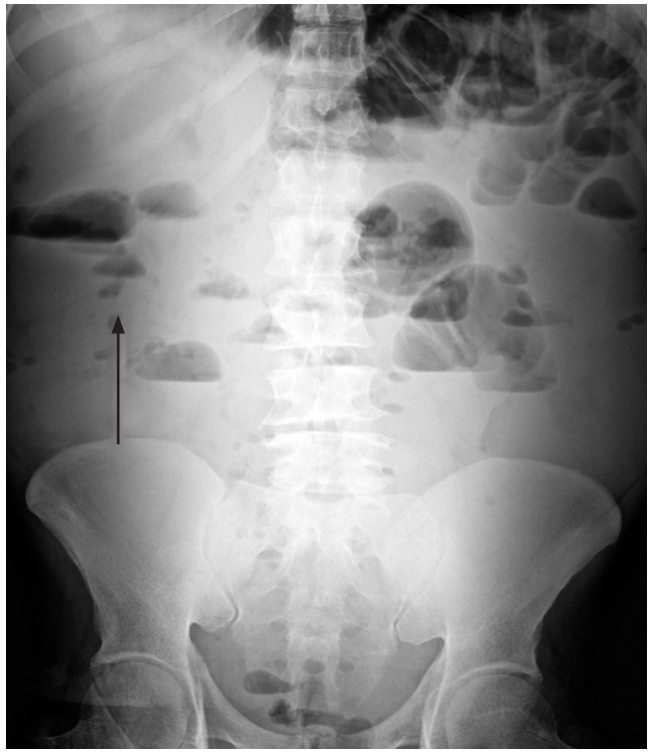

Figure 2. Simple x-ray showing multiple accumulations of gas and liquids (arrow) that compromise the entire abdominal cavity, especially in the mesogastrium and epigastrium, with air in the rectal ampulla (partial obstruction or ileus).

tous appearance, and areas of necrosis which were resected. End-to-end anastomosis was performed and washed with warm saline solution. The study of the surgical specimen identified diverticular formations with an inflammatory reaction (Figures 3 and 4).

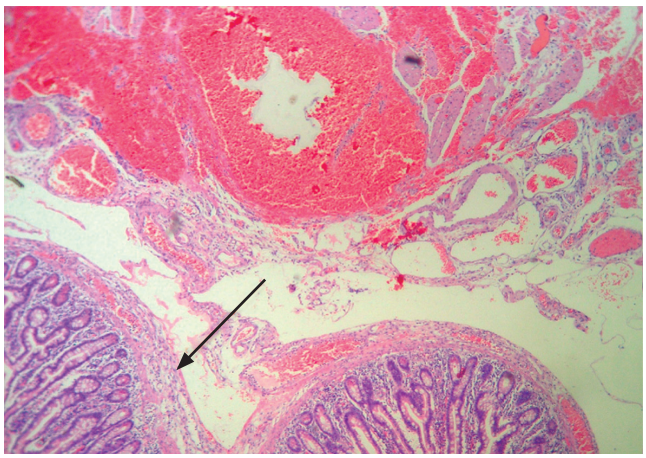

Figure 3. Segment of the jejunum in which edema and inflammation are most evident and appear together (arrow) with diverticular formations (hematoxylin-eosin 50 X).

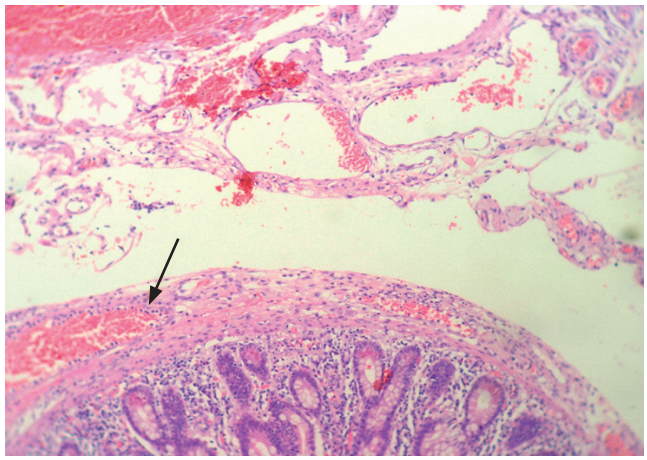

Figure 4. Segment of the small intestine in which there is edema of the wall with inflammatory infiltrate moving from the mucosa into the serosa. Bleeding can be seen beyond the serosa (arrow), but which does not adhere to it. It is probably related to bleeding in the peritoneum (hematoxylin-eosin 100 X).

The abdomen was initially operated on with the negative pressure system. Surgical washes were performed every 48 hours until the abdominal wall was closed on day 10. The patient was managed in the intensive care unit (ICU) for 6 days, then continued his favorable evolution in the general ward with resolution of abdominal sepsis, improvement of his clinical and mental condition, and recovery of functionality. He was discharged on day 14.

DISCUSSION

Acute abdominal pain, especially in the elderly population, is a frequent reason for consultation in the emergency department. A large percentage of these cases require hospital admission and/or surgical management. (11) This increases the cost of the health care system, especially when rapid diagnosis and timely intervention is not possible.

We present the case of an older adult described above who consulted for acute abdominal pain associated with psychiatric manifestations compatible with delirium. Clinically, we found data on systemic inflammatory response syndrome (SIRS) with a qSOFA score over two. (10) Paraclinical studies reported high levels of inflammatory reactants, the CBC had a left shift, and the patient had metabolic acidosis all of which supported the diagnosis of sepsis and merited a goal-guided intervention. (10) Images showed the rupture of a hollow viscera and signs of partial intestinal obstruction. (12) Due to the anatomical location of the pain, appendicular pathology was suspected, but the possibility of spontaneous perforation of the small intestine was not ruled out. The causes of spontaneous perforation of the small intestine appear in Table 1.

Table 1. Causes of spontaneous perforation of the small intestine (13)

Origin	Disease
Inflammatory/ obstructive	Diverticular disease (diverticulitis) (11) Crohn's disease
Autoimmune	Celiac Disease Graft-versus-host disease
Infectious	Viral: cytomegalovirus Bacteria: Salmonella and Mycobacterium tuberculosis Parasites: Ascaris lumbricoides
Induced by biological agents or medicines	NSAIDs Chemotherapeutic Immunobiological
Congenital	Meckel's Diverticulum Duplication of jejunum or ileum
Metabolic	Homocystinuria
Vascular	Microscopic polyangiitis Giant cell arteritis Radiation-induced vascular damage
Neoplastic	Primary: adenocarcinoma, others Secondary: melanoma, mesothelioma, others

Adapted from Freeman HJ. World J Gastroenterol. 2014; 20 (29): 9990-7

However, there is another way to approach acute abdominal pain in elderly patients based on probable etiological cause in obstructive, inflammatory, vascular or cryptogenic causes. (14) Age and case presentation were in favor of an inflammatory rather than a vascular condition. (15) Finally, pathology identified severe jejunal diverticular disease with signs of perforation (Figures 3 and 4).

Diverticular disease of the small intestine does not have well-established etiology, so multiple hypotheses have been posited. It was first described in 1794 by Sommering and confirmed almost 15 years later by Sir Astley Cooper. (16) It is most prevalent between 47 and 86 years of age with an average age of 72. (17) Its presentation is not specific but ranges from diffuse abdominal pain to lethal complications of all kinds, especially in the elderly among whom atypical onset such as delirium can occur. (18) Nevertheless, it is asymptomatic in 90% of cases when the duodenum is affected and in 40% of cases that affect the jejunum. In this last group it becomes symptomatic in 40% of cases. In these cases, its primary manifestation is intestinal malabsorption syndrome. (19)

Among its most frequent complications, the greatest risks come from intestinal obstruction and digestive bleeding which can result in formation of abscesses and, in rare cases, in fistulas and spontaneous perforation as a manifestation of acute abdomen, as in this case. (20) For this reason, it is important to expand differential diagnosis and remember that diverticula of the small intestine are always present.

Finally, the interesting thing to remember is that there are causes of acute abdomen that are not usually taken into account in assessment of geriatric patients. This is especially true when the onset of the condition is delirium, which has a potentially lethal organic cause.

Conflicts of interests

The authors declare that they have no conflicts of interest.

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None

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Laparoscopic-assisted transgastric retrograde endoscopic cholangiopancreatography in a patient with a Roux-en-Y gastric bypass: Case report and literature review

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Abstract
Obesity is a public health problem. Bariatric surgery plays an important role in the management of these patients. With the advent of bariatric surgical techniques, endoscopic digestive procedures, especially endoscopic retrograde cholangiopancreatography (ERCP), have become constant challenges. We describe a case of laparoscopic-assisted transgastric retrograde endoscopic cholangiopancreatography (ERCP) to treat calculi in the main bile duct of a patient with a history of a Roux-en-Y gastric bypass.

Keywords
Roux-en-Y gastric bypass, endoscopic retrograde endoscopic cholangiopancreatography (ERCP), laparoscopy.

INTRODUCTION

Obesity is a disease whose incidence has reached global epidemic proportions. It affects approximately 600 million people according to data reported by the World Health Organization (WHO). (1)

According to data from ASIS (Análisis de Situación de Salud - *health situation analysis*) of 2016; the prevalence of obesity in Colombia in 2010 was 20% higher than prevalence in 2005, having increased from 13 to 16 cases per 100 people. (2)

Although surgery is currently throughout the world as an effective option for long-term obesity control, these surgical techniques have made digestive endoscopic procedures constant challenges due to complications inherent in bariatric surgery. (3, 4)

Other Latin American experiences of laparoscopic retrograde endoscopic retrograde cholangiopancreatography (ERCP) have already been published, (5, 6) so the objective of this paper is to discuss the approach using this technique for managing bile duct stones in a patient with a history of Roux-en-Y gastric bypass (RYGB) surgery.

CLINICAL CASE

The patient was a 70-year-old woman who had undergone a gastric bypass in 2008 and laparoscopic cholecystectomy in 2013. She came to the hospital after having suffered abdo-

minal pain for one year. After magnetic resonance cholangiopancreatography (MRC) identified a 5 mm calculus at the distal end of the bile duct. The patient was hospitalized. Because of her history of RYGB which alters the anatomy and affects the usual endoscopic approach to the pathway bile, she was scheduled for laparoscopic-assisted transgastric endoscopic retrograde cholangiopancreatography (LAERCP).

Prior to laparoscopy to allow the duodenoscope to enter the stomach, the second duodenal portion where the major papilla is usually located was found (Figure 1). The extrahepatic and intrahepatic bile ducts were dilated and a calculus was found inside. The ducts were canalized and electrosurgical biliary sphincterotomy was performed. The bile duct was explored with a basket, and the calculus was extracted without complications.

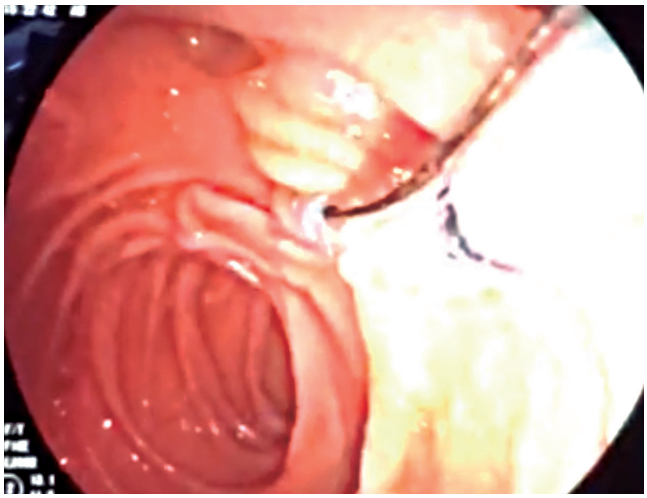

Figure 1. Major papilla and bile duct canalization with arch papillotome.

As of March 2018, the patient continued to be free of all digestive symptoms.

DISCUSSION

Rapid weight loss in patients who undergo RYGB is considered a risk factor for gallstone formation, (3) postoperative weight loss of more than 25% of original weight reportedly is associated with the formation of symptomatic gallstones, (7) and about 35% of patients develop biliary lithiasis in the first 12 months after bariatric surgery. (8)

Under normal conditions, ERCP is performed with a side-viewing duodenoscope inserted through the mouth and into the second portion of the duodenum to canalize the papilla. This successful technique combines endoscopy with radiological imaging. However, even in expert hands complications including bleeding, perforations, cholangitis and pancreatitis can occur. (9) For this reason, ERCP is considered an advanced endoscopy technique that requires special training. (10, 11)

The difficulties and complications inherent to ERCP increase when performed in altered anatomy. When ERCP is performed in patients with altered anatomy, important challenges determine the procedure's success rate. These include ability to intubate the duodenum, ability to face the major papilla, ability to enter and canalize the major papilla, therapeutic success, total time of intervention, and complications inherent to the procedure. Due to these difficulties, ERCP should be performed at referral centers for advanced endoscopy with the support of a multidisciplinary team of gastroenterologists, radiologists, surgeons and anesthesiologists who can facilitate success and mitigate the number of complications. (8)

There is no protocol on how to perform ERCP in postbariatric surgery patients, and different types of endoscopes and endoscopic techniques can be used depending on availability and local experience. (11) Nevertheless, recommendations for performing ERCP in patients who have altered anatomy have recently been published. (12) For patients with Billroth II anatomy, biliary access is similar with front and side view endoscopes, but the latter are associated with increased risks of perforation. (12) In these cases, the major papilla can be reached since the afferent loop is relatively short, but the main challenges of duodenal intubation and entry into the bile duct remain. A series of 713 patients has demonstrated a success rate for duodenal intubation of 86% and a success rate for bile duct canalization of 94%. The overall perforation rate was 1.8%. (13)

ERCP assisted by single or double balloon enteroscopy is one of the recommended options for patients who have undergone RYGB. The ERCP technique assisted by double balloon enteroscopy consists in advancing through the small intestine by inflating and deflating balloons until the major papilla is reached allowing canalization of the bile duct. A multicenter study of 159 ERCPs performed in 129 patients who had undergone RYGB found 69% duodenal access with double balloon enteroscopy and 72% with simple enteroscopy. The ERCP success rate was 88%. (14)

A recently published metaanalysis covering 15 clinical trials with 461 patients has evaluated diagnostic and therapeutic success of ERCP assisted by simple enteroscopy in patients who had undergone RYGB, hepaticojejunostomy or the Whipple procedure. In general, the success rate for ERCP by simple enteroscopy was 81% with an adverse event rate of 6.5%. (15)

Since oral access is difficult in patients who have undergone gastric bypasses and ERCP assisted by enteroscopy has disadvantages such as long duration of the procedure, difficulty orienting endoscopy equipment, less maneuve-

rability of equipment, and availability of reliable and useful accessories for increasing the diagnostic and therapeutic performance of the procedure, an alternative method has been devised. This consists of reaching the major papilla through the stomach with laparoscopic assistance. Transgastric ERCP assisted by laparoscopy, originally described by Baron, (3) has been shown to be superior to ERCP assisted by enteroscopy in terms of duodenal intubation, identification of the major papilla, bile duct canalization rates, therapeutic success and total time of procedure. No statistically significant differences were found in relation to hospitalization stays and complication rates. (16, 17)

Recently, Snauwaert has published a retrospective, multicenter observational study of a cohort of patients with histories of RYGB who also presented complicated biliary pathologies including cholangitis, choledocholithiasis and biliary pancreatitis. The patients had all undergone laparoscopic-assisted transgastric ERCP between 2008 and 2014. A total of 23 patients had undergone the procedure, with a bile duct canalization success rate of 100%; without complications (bleeding, pancreatitis or perforation) and with an average hospital stay of 2.8 days (range: 2-4). (18)

In recent years, another endoscopic technique has also been used to perform ERCP in patients who had undergone RYGB,. This technique uses endoscopic ultrasonography (EUS) to gain access to the excluded stomach and perform transgastric ERCP. This procedure is performed in two stages during separate endoscopic sessions. The first stage consists of identifying the gastric remnant through EUS and placing a gastrostomy tube. The second stage consists of removing the gastrostomy tube and placing a metal stent through the fistula to allow introduction of the duodenoscope for performance of the ERCP. A study of six patients who underwent this procedure has shown that EUS guided access to the gastric remnant was successful in 100% of the cases. The average time of the procedure was 81 minutes. Antegrade ERCP was successfully performed in all six patients, with the two stages separated by an average of 5.8 days. (19)

In our case, the bile duct was successfully canalized, a biliary sphincterotomy was performed, the bile duct was explored with a basket, and the stone was removed without complications. The patient evolved satisfactorily and was discharged at 72 hours.

In conclusion, the laparoscopic transgastric approach offers advantages including rapid access to the duodenum and adequate visualization of the papilla. This allows the use of a side view duodenoscope which increases both diagnostic and therapeutic performance. This approach also offers the possibility of subsequent access if required. Although surgical intervention is sometimes necessary, laparoscopic gastrostomy is associated with low rates of morbidity and mortality. For this reason, transgastric ERCP assisted by laparoscopy is a safe and successful method for management of biliary pathology in patients with modified anatomy following RYGB.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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Familial adenomatous polyposis and colorectal cancer prevention: A case report

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Abstract

Familial adenomatous polyposis (FAP) is a hereditary disease characterized by the growth of multiple colorectal epithelial adenomas. It is an autosomal dominant disorder caused by an APC gene defect. Degeneration to colorectal cancer is considered unavoidable in these patients if they do not receive adequate therapeutic management.

We present the case of a 25-year-old female patient consulted after a change in her evacuation pattern and abdominal pain. She had no relevant family history associated but based on results of paraclinical tests diagnosis of FAP was made for which therapeutic management was implemented. This is a case report with a literature review and update of the topic highlighting clinical issues related to recognition of the disease and issues that should be taken into consideration for the prevention of cancer in patients with FAP.

Keywords

Familial adenomatous polyposis, cannula.

INTRODUCTION

Familial adenomatous polyposis (FAP) is inherited through transmission of an autosomal dominant pattern characterized by an APC gene defect located on the long arm of chromosome 5q21. (1-5) Only 25% to 30% of FAP patients do not have clinical or genetic evidence of the disease among family members. (6) The incidence of documented FAP in family records ranges from 1 in 7,000 to 1 in 16,000 live births and represents approximately 0.5% of all colorectal cancers. (4) The average age of onset is 16 years and the progression to colorectal cancer (CRC) occurs from the age of 40 to the age of 50 years with almost complete penetrance. (5, 7)

The appearance of hundreds or thousands of polyps on the rectal, colonic, duodenal and/or gastric mucosa is the primary manifestation of the disease. (8, 9) Polyps have tubular, villous or mixed glandular histological structures, but the size of the polyps, rather than their structures, is the most significant predictive factor for the onset of cancer. (10) FAP usually has extracolonic manifestations such as gastric and small intestinal polyps. (1) Extraintestinal manifestations can include congenital hypertrophy of the retinal pigment epithelium, diffuse mesenteric fibrosis (desmoid tumors), osteomata of the lower jaw (in 90% of cases), skull and long bones (a phenotypic variant known as Gardner's syndrome), and various dental abnormalities. (11) Neoplasms such as medulloblastoma (Turcot's syndrome) can also occur in the central nervous system, thyroid glands, hepatobiliary system and adrenal glands. (7, 8, 12)

The most important diagnostic approach to FAP is screening of patients with family histories even though it is believed that one third of all cases are due to de novo mutations. (13, 4) Patients without any family history present great diagnostic challenges with negative prognostic implications. Surgical treatment aimed at preventing development of CRC is indicated when FAP is diagnosed, especially

when the risk of onset is very high. (14) Development of CRC is inevitable when the disease follows its natural course in patients who do not undergo surgery. (1, 14, 15)

CASE PRESENTATION

The patient was a 25-year-old woman who had suffered from bloody stools and abdominal pain for a month prior to admission. Usually in the morning, she had one bloody stool without mucus or diarrhea followed by intense colic lasting for approximately one hour. Her defecation pattern changed from three/day to one/day.

Personal and Family Background

She was endoscopically diagnosed with chronic gastritis at the age of 13 when a single sessile polyp was found. One grandmother had died at age 69 from breast cancer. Her other grandmother was alive and had rheumatoid arthritis. Her mother was alive and had been diagnosed with uterine fibroids. The patient had no knowledge of any family history of CRC, polyps or FAP.

Physical Examination

The patient weighed 45 kg, was 168 cm tall, and had a body mass index (BMI)of 15.9. Her abdomen was flat, soft, depressible, painful on deep palpation of the lower hemiabdomen, with no signs of peritoneal irritation or visceromegaly and with sounds of liquid and air. Rectal examination was not painful and found normal muscle tone and temperature of the anal sphincter and rectal walls with multiple palpable masses of different diameters. The rectal ampulla contained pasty stool and the tip of the glove showed a small amount of blood. The rest of the evaluation was within normal limits.

Paraclinical Tests

A complete blood count and blood chemistry were normal. In addition, barium enema abdominal radiography found alterations of the colonic frame with accumulation of secretion (Figure 1). In the rectosigmoidoscopy, more than 100 polyps of sizes ranging from 3 mm to 5 cm were observed from the distal ascending colon to the rectum. Some were pediculate and others were sessile, tubular and villous in appearance (Figures 2 and 3).

A gastroduodenoscopy showed white cottony points in the second portion of the duodenum with multiple sessile polypoid lesions in the corpus and fundus (Figure 4).

The histopathological study shown in Figure 4 reported that:

- The mucosa of the sigmoid colon had tubular adenoma with high grade focal dysplasia (10%).
- There were tubular villous polyps in the transverse colon polyps and adenoma with a predominance of the adenomatous component in 80% of the material examined plus areas of high grade focal dysplasia.

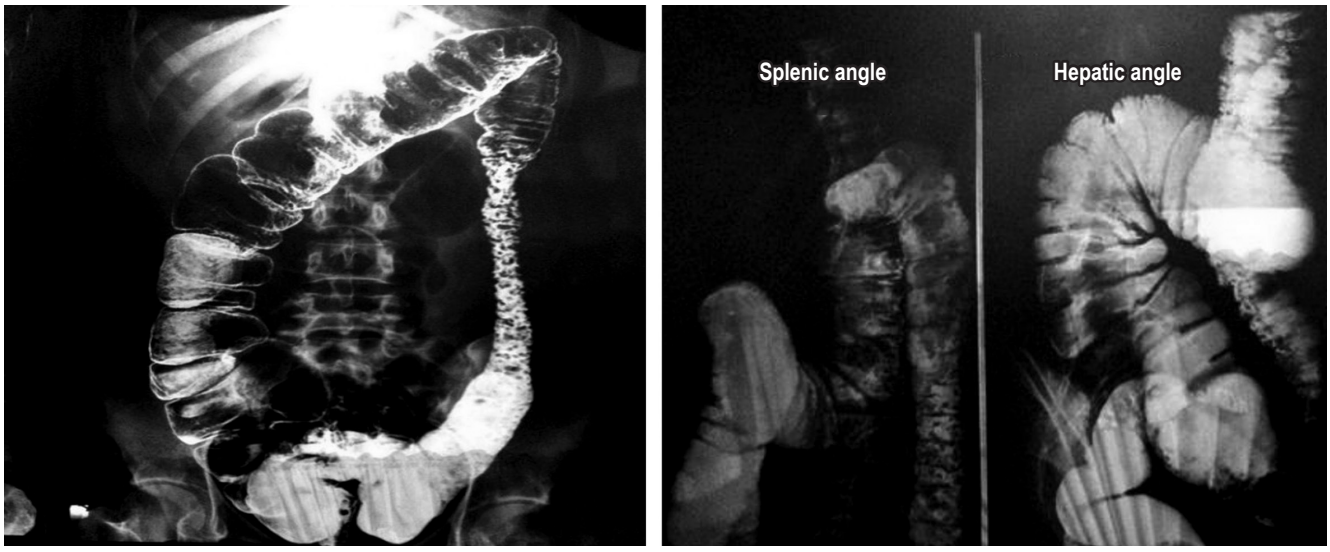

Figure 1. Abdominal barium enema radiography in standing anteroposterior projection shows evidence of colonic wall thickening, irregular dilations of the colonic frame, increased amounts of heterogeneous secretions in the ascending colon, hepatic angle, descending colon and sigmoid colon with multiple polypoid images and correlative signs with collar ulcers.

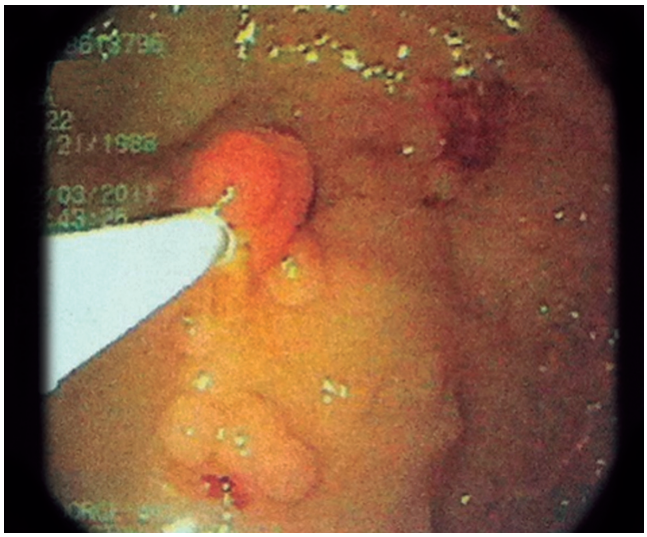

Figure 2. Rectosigmoidoscopy. A tubular pedicled polyp can be seen.

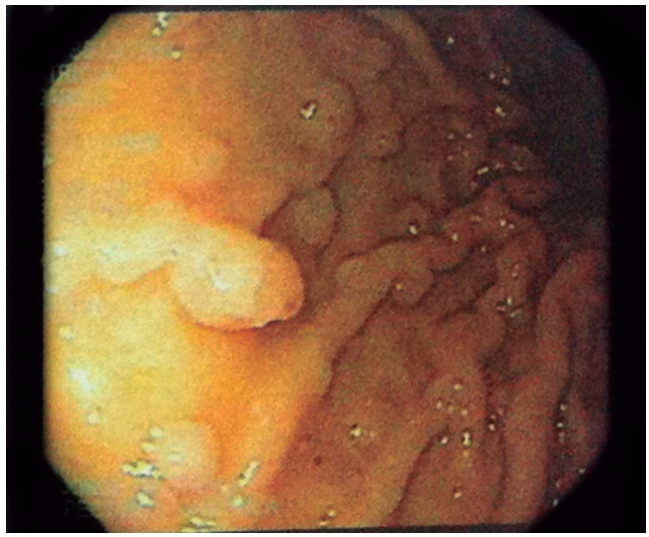

Figure 3. Rectosigmoidoscopy shows multiple sessile villous polyps of various diameters.

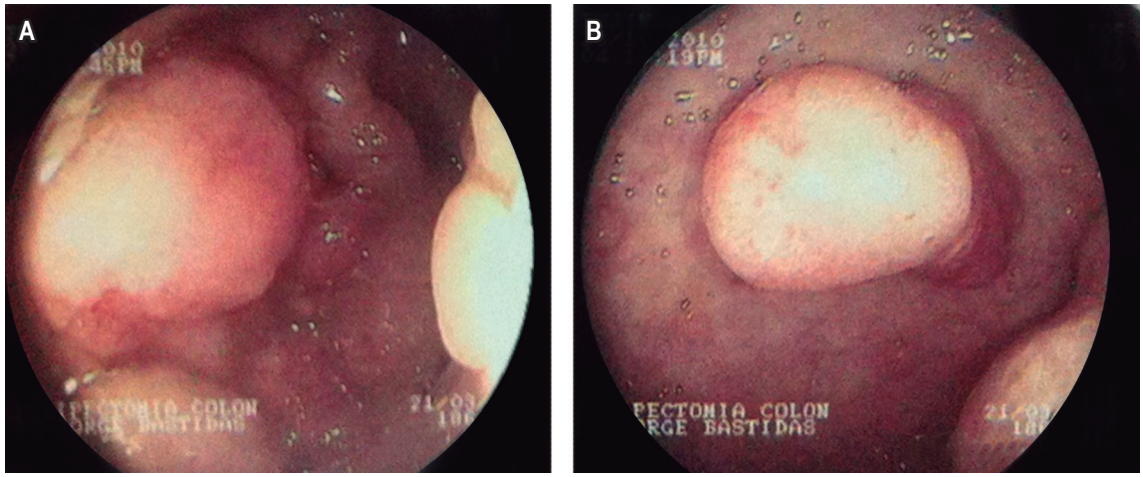

Figure 4. Gastroduodenoscopy. (A) Fundus (B) Corpus with multiple sessile polyps of various diameters.

- Hyperplastic oxyntic gland adenoma with dilation of glandular crypts and chronic mucosal inflammation in the gastric corpus.

According to the clinical and the complementary evidence, a diagnosis of FAP was established.

Treatment and Evolution

A total colectomy plus resection of the upper two thirds of the rectum with an ileorectal anastomosis was indicated. First intervention, a protective ileostomy was placed. Pathological analysis of ileal, colonic and rectal tissue obtained showed countless polypoid structures mostly consisting of pediculate and sessile tubulovillous adenomas with evidence of high-grade dysplasia seated on the mucosa with multifocal hyperplastic changes. This intervention evolved favorably.

The patient was re-admitted six months later for scheduled end to end anastomosis. Paralytic ileus developed in the immediate postoperative period but was successfully treated medically. In the year after surgery, the patient had three episodes of intestinal obstruction that merited surgical resolution. In the last episode, an intra-abdominal abscess in the right iliac fossa led to placement of a Bogotá bag which required hospitalization for 8 months. The patient's condition evolved favorably, and she is currently is

in good general condition with regular intestinal transit and without any other type of compromise.

DISCUSSION

Although FAP has been disease studied and described, prevention and early diagnosis are key for the prognosis, and in this lies the relevance of this review considering that all untreated cases evolve toward in malignancy. (13) Diagnosis is based on clinical and endoscopic evidence. (12) The most common symptom is blood in the stool (occult or visible) mainly because polyps bleed into their stroma as more and more polyps progressively appear. (1, 8) Other possible symptoms are flatulence, changes in defecation pattern, and post-defecation colic in the lower hemiabdomen. (7, 8) Anorectal examination may show polyps if they prolapse through the rectum. (1) Family history is also of great importance, so the patient should be asked about family history of colonic polyps and/or colon cancer. (15) Nevertheless, about one third of these patients do not have any related family history, as in the case of our patient.

The diagnosis is established by clinical criteria by means of a barium enema and a total colonoscopy which can show evidence of larger lesions and be used to take biopsy samples to rule out malignancy. (16) This differentiates the disease into either its classical variation of more than 100 polyps or into its attenuated variation with less than 100 polyps. (7) A search for extracolonic findings, especially duodenal polyps and epithelial hyperpigmentation of the retina, is necessary. The latter is observed in 83% of families with FAP. (7, 17) Screening of relatives and identification of the APC gene are both important although genetic study of this patient was not possible for socioeconomic reasons. (2, 14)

Surgery is the fundamental pillar for management of FAP, particularly when there is a mutation between codons 1251 and 1309 which express the most serious phenotype. (13) Individualization of each patient and genotype-phenotype correlation are important for choosing among surgical options which include total proctocolectomy with permanent ileostomy, colectomy with ileorectal anastomosis (IRA), and proctocolectomy with ileal pouch–anal anastomosis (IPAA). The first approach is not performed prophylactically and is indicated in patients with extensive rectal polyposis, cancer of the distal rectum and for those for whom follow up is impossible. On the other hand, the IRA colectomy and the IPAA proctocolectomy are prophylactic techniques carried out in asymptomatic patients who have been identified as being at risk by genetic tests or predictive colonoscopy. However, the risk of developing cancer in the preserved rectal portion after 20 years is 25%, so periodic monitoring must be particularly strict. (13, 18)

Medical treatment can be considered for easily monitored patients with the attenuated variant with less than 20 rectal polyps whose size is less than 5 mm. (19, 20) The use of non-steroidal anti-inflammatory drugs (NSAIDs) such as sulindac and celecoxib has been shown to be the most efficient at reducing the amount and size of colorectal adenomas characterized by high levels of cyclooxygenase 2 (COX-2) expression. (20, 21) Their use is accepted as adjuvant therapy to surgical treatment but not as an alternative. (22) Surgical resolution is controversial in asymptomatic patients for whom intervention is recommended at the end of adolescence. (14)

In at-risk individuals with evidence of polyposis without PAF or its attenuated variant, annual colonoscopy or flexible sigmoidoscopy is suggested from onset of puberty. (5, 10, 19) Colonoscopic follow up of patients who have undergone IRA colectomy should be initiated six months after surgery and thereafter be done once a year. The initial follow-up is the same for proctocolectomy patients with IPAA with subsequent follow-up every two or three years. (18, 22). This periodicity is conditioned by baseline and follow up findings of the number, size and histology of adenomas as well findings of any symptoms or mutations in the APC gene. (10)

The close relationship of exhaustive study of each patient with correct therapy choices and good prognoses demonstrates the crucial role of permanent analysis of diagnostic guidelines and constant investigation of the subject since about 30% of patients with this disease have no relevant family history. (4) As in the case presented, absence of family history can result in diagnosis at a later age after symptoms develop which implies increased risks of morbidity, mortality and development of CRC. (4) Additional studies of the genetics and epidemiology of patients without family history could improve the bases of diagnosis and clinical management.

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