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Acceptance, yield and feasibility of attaching HCV birth cohort screening to colorectal cancer screening in Spain

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ABSTRACT

Introduction: The US Centers for Disease Control recommends hepatitis C virus (HCV) screening for baby boomers. Spain presents a similar distribution of infected patients. We performed a cross sectional prospective study to evaluate the prevalence of undiagnosed HCV infection in subjects born between 1949 and 1974.
Methods: All out-patients within the age range, both symptomatic and screening procedures, undergoing colonoscopy between December 2014 and June 2015 were offered a HCV antibody blood test and a survey including risk factors for HCV infection and attitude toward HCV screening. Patients with chronic HCV or with a previous negative HCV antibody test were excluded.
Results: A total of 570 subjects, 50% screening procedures, were analyzed. The median age was 55.7, 94.6% were born in Spain and 54.6% were women. Antibodies against HCV were found in 1.6% (95% CI: 0.8–3%) and HCV-RNA in 0.4% (0.1–1.3%). We found no statistically significant differences regarding HCV prevalence, risk factors or socioeconomic characteristics between subjects undergoing colorectal cancer screening and symptomatic subjects.
Conclusion: Symptomatic and screening subjects undergoing colonoscopy support HCV screening and present a similar HCV risk profile. Results suggest linking colorectal and HCV screening would yield good results.

1. Introduction

Hepatitis C virus (HCV) is a global burden, with approximately 170 million infected worldwide [1]. Serological and polymerase chain reaction tests allow a straightforward diagnosis, but a significant group of patients remain undiagnosed due to various motives: Liver function tests are frequently within normal limits, over 15% of infected patients do not acknowledge any risk factor [2], and it is asymptomatic for decades, until liver damage is severe. Fortunately, progression to cirrhosis is not universal. Cirrhosis is present in 16% of patients 20 years after diagnosis and in up to 40% after 30 years [3].

In Europe, serology based studies suggest a 0.1–3.2% prevalence [4]. In Spain estimates range within these limits, between 0.7% and 2.6% [5–11]. In these studies, published between 1996 and 2002, seroprevalence distribution displayed two peaks. The first one included subjects 20–45 years old and the second one subjects over 65.

In 2012 the Centers for Disease Control and Prevention (CDC) recommended all persons born between 1945 and 1965 in the USA should be tested once for HCV antibodies (HCV Ab) [12]. This cohort has the highest HCV prevalence in the country, most of them have been infected for at least 20 years, and a considerable proportion is undiagnosed [2,13]. Thus, it is the cohort with the highest proportion of subjects with a significant (over 10%) risk of cirrhosis.

Our country does not have a nationwide recommendation concerning HCV infection screening. Based on the epidemiological similarities between our country and the USA, we designed a study to estimate the prevalence of undiagnosed HCV infection in the cohort of patients at highest risk, those born between 1949 and 1974. We also evaluated the possibility of linking this screening to other nationwide health promoting programs,

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namely colorectal cancer screening, and its acceptance by general population.

2. Methods

This cross sectional prospective study was conducted between December 2014 and June 2015 at our University Hospital, which belongs to the Madrid Health Service (Servicio Madrileño de Salud – Sermas) and attends a population of approximately 225,000. The local ethics committee approved the project in August 2014. All authors had access to the study data and have reviewed and approved the final manuscript.

2.1. Patient selection

All consecutive patients scheduled for out-patient non-urgent colonoscopy between the first of December 2014 and the fifth of June 2015 were evaluated. The only inclusion criterion was a birth date between the first of January 1949 and the thirty-first of December 1974. Both screening and symptomatic patients were included. Exclusion criteria were: known hepatitis C infection, at least one previous negative test for HCV Ab and refusal to take part in the study. Previous HCV Ab tests were manually searched for all candidates in our center's database, which covers since June 2004 and includes analysis ordered by primary care providers and hospitalists. Subjects with previous HCV Ab tests performed in any other setting (e.g. blood donors, healthcare workers, tests performed in other institutions, etc.) were also excluded.

2.2. Sample management

Blood samples were obtained in the endoscopy unit, taking advantage of the intravenous catheter placed for sedation. Samples were stored at room temperature until each working shift was finished. They were then submitted to the laboratory, where they were stored at 4 °C.

HCV Ab testing was performed using the Access HCV Ab PLUS EIA (Bio-Rad, Marnes-la-Coquette, France) in a UniCel®DxI800 platform, according to manufacturer's instructions. In this chemiluminescent immunoassay, a solid phase coated by the NS3, NS4 and from the capsule recombinant peptides captures specific IgG and IgM antibodies anti HCV present in the sample. After a conjugation with anti-antibodies conjugated with alkaline phosphatase, a chemiluminescent reaction occurs upon the addition of a specific substrate. Therefore, HCV Ab concentration is proportional to the intensity of the luminescent signal produced by the enzymatic reaction.

Serological confirmation of the presence of HCV Ab concluded by the initial screening test was performed by the INNO-LIA HCV Score (Fujirebio Europe N.V., Gent, Belgium) following manufacturer's recommendations. This 3rd generation line immunoassay incorporates HCV antigens derived from the core region, the E2 hypervariable region, the NS3 helicase region and the NS4A, NS4B and NS5A regions, which are coated in 6 lines on a nylon strip. After incubation with the sample, a specific enzyme immunoassay is performed on any given line. If the individual tests fulfilled the validation criteria proposed, we followed the manufacturer's instruction for the interpretation of the results.

HCV RNA detection and quantification was performed on a COBAS AmpliPrep/COBAS TaqMan HCV quantitative test v2.0 (Roche Molecular Systems, Inc., Branchburg, NJ), following manufacturer's instructions. This test uses magnetic silica bead-based nucleic acid extraction by Cobas AmpliPrep, followed by a selective amplification with primers specific to the 5′ UTR of the HCV genome using uracil-N-glycosylase and deoxyuridine triphosphate; detection of the amplified target and a quantitative standard is achieved by dual-labeled fluorescent probes that allow for real-time detection of PCR product accumulation by monitoring the emission intensity of fluorescent reporter dyes released during amplification process.

2.3. Questionnaire

All subjects presenting the inclusion criterion received information about the study nature and its aims via a telephone call the week before colonoscopy. Informed consent was obtained the day of the colonoscopy. Questionnaires were performed on the same day. Questions regarding the presence of known risk factors for HCV were presented in a yes/no manner, except the number of sexual partners which was presented using intervals. Demographic data included age, sex, nationality, educational attainment and annual house income, which was assessed using intervals. To assess the willingness to participate in a hypothetical HCV screening program if it implied an additional blood test, we used a 5 point Likert scale question.

2.4. Definitions

Chronic hepatitis C was defined as the presence of HCV RNA, which was performed only if the first HCV Ab test was positive. Subjects with a positive result in both serological assays were defined as seropositive. Those with a positive first test and a negative confirmatory assay were considered as false positives. Questionnaire responders were defined as those subjects leaving only 4 or less questions (including all survey items) unanswered. Symptomatic patients were defined as those undergoing colonoscopy due to symptoms (diarrhea, rectal bleeding, etc.) or signs (anemia, iron deficiency, etc.) suggesting gastrointestinal disease. Asymptomatic patients included those undergoing colorectal cancer screening or polyp surveillance.

2.5. Objectives and outcomes

Our primary endpoint was estimating the prevalence of undiagnosed HCV infection in subjects born between 1949 and 1974. Secondary aims were to describe the attitude toward HCV screening in our population and to identify seroprevalence differences and presence of discrepant risk factors between symptomatic patients (representing general population) and patients in screening programs.

2.6. Sample size and bias assessment

According to previously published studies, we estimated a 2.5% prevalence of hepatitis C in our region in subjects born between 1949 and 1974. We calculated a sample of 555 subjects would be needed to estimate the real prevalence of undetected HCV chronic infection in our population with a 95% confidence and a 0.013 precision. Assuming a proportion of withdrawals and sample mishandling of 5%, we finally defined a sample size of 582 subjects.

We considered a sample selection bias a probable risk. Invited subjects were active users of the National Health Service so we considered they presented a higher probability of having being tested for HCV Ab than general population. In the subgroup of already tested, those presenting HCV infection have frequent out-patient clinic visits and analysis. Thus, they present a higher risk of being submitted to colonoscopy, so we decided to exclude them. Those with a previous negative HCV Ab were also excluded to avoid blunting our estimations, as the subgroup of previously tested had a spurious 0% prevalence of HCV infection after excluding those with HCV infection. Thus, we decided to exclude all previously tested. Data regarding the place of birth, educational attainment and the