

ORIGINAL ARTICLE

Prospective study of cross-infection from upper-GI endoscopy in a hepatitis C-prevalent population

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Background: A high prevalence of hepatitis C (HCV) in the Egyptian Nile Delta increases the demand for upper-GI endoscopy (UGIE) and the risk of cross-infection with this virus.

Objective: To assess the potential for UGIE to transmit HCV when endoscopes are reprocessed according to current international standards.

Design: A prospective cohort study to detect the incidence of HCV and hepatitis B cross-infections.

Setting: The endoscopic unit of the National Liver Institute, a hospital for patients with chronic liver disease.

Patients: A total of 859, including 149 of 249 patients (60%) at risk (HCV-antibody negative) retested 3 to 10 months after UGIE with endoscopes previously used on HCV carriers.

Interventions: Nurses were trained to process endoscopes according to American Society for Gastrointestinal Endoscopy guidelines, and procedures were observed and recorded.

Main Outcome Measurements: Seroconversions were determined by using enzyme immunoassays for anti-HCV; reverse transcriptase-polymerase chain reaction was used to detect HCV-ribonucleic acid (RNA).

Results: Four patients, initially negative, tested positive for anti-HCV after UGIE. However, 2 of these had HCV-RNA in their baseline blood sample, and the other 2 did not have HCV-RNA in their follow-up sample.

Limitations: Very-high prevalence of anti-HCV in subjects reduced the proportion at risk of infection, and follow-up was difficult.

Conclusions: There were no cases of proven transmission of HCV when endoscopes were reprocessed by using currently accepted standards. This negative study is encouraging, because patients undergoing UGIE in the Nile Delta of Egypt where HCV-caused liver disease is so pervasive would be at maximum risk of HCV cross-infection from UGIE. (*Gastrointest Endosc* 2007; ■: ■-■.)

Cross-infections involving a wide variety of pathogens, including hepatitis C virus (HCV), have been reported when using flexible endoscopes for diagnostic and therapeutic procedures.¹⁻⁴ This unacceptable complication encouraged the adoption of numerous guidelines for preparing endoscopes for reuse (reprocessing) to prevent cross-infection during endoscopy.⁵⁻¹⁰ The issues regarding reprocessing of endoscopes between procedures focused on cleaning debris from the previous procedure, the chemosterilant used, and the immersion time and temperature.¹¹⁻¹⁵ Professional societies generally recommend

a shorter, 20-minute, chemical disinfection with 2.4% glutaraldehyde at 20°C rather than the 45-minute exposure at 25°C in the U.S. Food and Drug Administration (FDA) requirements.^{5-10,13,15}

Compliance with U.S. guidelines, which have been widely adopted internationally, and FDA requirements, however, has been variable and historically poor.^{13,16} A national survey reported that only 11% of gastroenterologists who used 2% glutaraldehyde to reprocess endoscopes followed FDA guidelines.¹⁶ FDA inspections in 1995 found that only 5% of 80 endoscopy clinics properly dried endoscopes to prevent growth of bacteria during storage, and almost half had at least 1 patient-ready endoscope visibly encrusted with patient matter.¹¹

Egypt has an exceedingly high reservoir of HCV infection, making exposures to blood and other human biological fluids much more risky than under similar conditions in the United States and elsewhere.¹⁷ HCV is estimated to attribute to 70% to 80% of hepatic fibrosis, cirrhosis, and hepatocellular carcinoma in the country.¹⁸⁻²⁰ Complications of both *Schistosoma mansoni* and HCV infections are highly prevalent in the rural population that receives medical care at the National Liver Institute (NLI); complications of both infections often cause hemorrhage from bleeding esophageal varices.²⁰ Both diagnostic and therapeutic, ie, sclerotherapy, upper-GI endoscopy (UGIE) are frequently conducted in the NLI Endoscopy Unit. Therefore, we concluded that this provided a unique site for conducting a prospective cohort study of cross-infection with HCV during UGIE; the results of this investigation are reported herein.

PATIENTS AND METHODS

Study design and subjects

The project was approved by the institutional review boards of both the University of Maryland Baltimore and Menoufiya University's NLI. All subjects provided informed consent and information on demographics, medical history, presenting symptoms, and any potential risk factors for blood-borne pathogens. We also obtained information on diagnoses, UGIE findings, and clinical outcomes. Blood samples for determining antibodies to HCV (anti-HCV) were collected from 2000 to 2004 in a cohort of 859 subjects immediately before the endoscopy (653 diagnostic, 206 therapeutic). Starting in 2002, we only admitted to the study patients undergoing diagnostic UGIE, because those having therapeutic sclerotherapy had such a high prevalence of anti-HCV that very few of this group would be at risk of infection.

Follow-up blood samples were collected from 149 subjects 2.8 to 10 months (median, 3.6 months) after the UGIE, and an interim questionnaire was administered to obtain information on their medical status and potential exposures to blood-borne infections during the interval. An aggressive protocol was developed to locate and retest subjects who were initially anti-HCV negative (patients at risk for HCV infection), which included contacting them to request that they return to the clinic and, in some cases, visiting them in their homes.

The 149 subjects initially anti-HCV negative were sex- and age-matched with subjects from a village with a 24% prevalence of anti-HCV in the same area of the Nile Delta.^{21,22} These control subjects all had follow-up enzyme immunoassay for anti-HCV testing performed, allowing seroconversion rates to be calculated.

Laboratory procedures

Sera collected at the time of the procedure and from those returning for follow-up was stored at -80°C . Anti-

Capsule Summary

What is already known on this topic

- Cross-infections involving a variety of pathogens, including HCV, have been reported when using flexible endoscopes for diagnostic and therapeutic procedures, resulting in numerous guidelines for preparing endoscopes for reuse.

What this study adds to our knowledge

- In a single-center prospective cohort study of 859 patients, including 249 patients who were HCV-antibody negative, there were no cases of proven transmission of HCV when endoscopes were reprocessed by using currently accepted standards.

HCV and HCV-RNA was tested in all initial and follow-up blood samples. Enzyme immunoassays (EIA) for anti-HCV (HCV EIA 3.0) and hepatitis B (HBV) surface antigen (HBsAg and Auszyme monoclonal; Abbott Laboratories, Chicago, Ill) were performed by following the manufacturer's instructions. An in-house direct reverse transcriptase-polymerase chain reaction (RT-PCR) was used to detect HCV-RNA.²³ If a serum sample was positive for anti-HCV and negative for HCV-RNA, then the RT-PCR was repeated after extraction of the HCV-RNA before the results were considered negative. All EIA and RT-PCR tests having conflicting results were repeated. It is our laboratory practice to repeat the testing a third time if the results of the second testing differed from the first. However, this was not necessary in this case. We routinely use 9 controls when we perform RT-PCR. These include a high-, medium-, and low-titer HCV-RNA positive sera. If there are any discrepancies in the test results among the controls, including not detecting HCV-RNA in the low-titer positive control, then the entire plate is retested at another time.

Reprocessing endoscopes

The flexible endoscopes (gastrosopes) used in the study included models having internal channels accessible to brushing (Pentax FG 29W; Pentax Corp, Tokyo, Japan) and others having air and water channels not fully accessible to cleaning with a brush (2 types, both with double channels; Olympus Corp, Tokyo, Japan). All endoscopes were meticulously cleaned before each procedure and then manually exposed to 2.4% glutaraldehyde for a minimum of 20 minutes, following guidelines published by the American Society for Gastrointestinal Endoscopy (ASGE) and the Society of Gastroenterology Nurses and Associates (SGNA).⁸ Sterile disposable biopsy forceps (Microvasive Endoscopy, Boston Scientific Corp, Natick, Mass) were used for biopsies, and disinfectant solutions were maintained at pH 9.5, under ambient temperature conditions (mean [standard deviation], $21^{\circ}\text{C} \pm 4.6^{\circ}\text{C}$).

Quality control

Nurses in the endoscopy unit were trained to follow ASGE/SGNA reprocessing guidelines and were supervised by an infection-control nurse (A.E.-B.) who received her doctorate at the University of Maryland's School of Nursing. The nurse (A.E.-B.) oversaw all UGIE procedures and recorded whether any deviations from these guidelines occurred during reprocessing. Some of the recorded details included pH, temperature, and activity of glutaraldehyde solutions and exact exposure times. Each procedure was described in detail, including estimating the amount of bleeding and recording any breaches in infection-control procedures during UGIE.

RESULTS

Of the 859 patients admitted to the study, 206 had sclerotherapy for bleeding esophageal varices (88% were anti-HCV positive), and 653 had diagnostic examinations (66% were anti-HCV positive). The overall prevalence of anti-HCV in the cohort was 71%; 149 of 249 at-risk (ie, initially anti-HCV negative) patients (60%) provided follow-up data and blood samples.

Results of blood samples collected at the time of endoscopy and at the follow-up visit indicated that 4 patients who were previously anti-HCV negative seroconverted and that the individuals endoscoped with the same instruments before them were both anti-HCV and HCV-RNA positive. However, 2 patients who seroconverted, in blood samples taken 3 and 3.5 months after the procedure, had been HCV-RNA positive in their initial blood sample taken at the time of UGIE. The seroconversion rate in the sex- and age-matched controls was 10.2, 95% confidence interval 0.0-21.8 per 1000 person years of observation, or 1% per year.

Only 2 patients who were anti-HCV negative, a 35-year-old woman and a 56-year-old man, therefore, had serologic findings compatible with possible HCV-infection occurring during UGIE. Both patients underwent endoscopy with instruments having internal air and water channels that were inaccessible to brushing. However, neither of them had HCV-RNA in their follow-up sera taken 3 and 6 months after the procedure. Moreover, because RNA was not present in the follow-up samples, genotyping and sequencing could not be used to confirm whether patients who previously underwent endoscopy were the source of their infections.

In addition, none of the 30 patients who were seronegative who underwent endoscopy after patients who were HBsAg positive (3.5% of 859 patients) seroconverted.

DISCUSSION

In the endoscopy unit at the NLI, the high reservoir of HCV infections in patients bleeding from esophageal vari-

ces seemed to provide an ideal cohort to determine the potential cross-infection during UGIE. If 50% of those being endoscoped were anti-HCV positive, we estimate that 40% would also have HCV-RNA, and thus be potentially infectious to the next anti-HCV negative patient examined with the same endoscope. However, the prevalence of anti-HCV was even higher, leaving only about 30% at risk of infection, even after we discontinued admitting patients who were undergoing sclerotherapy, a group with an 88% prevalence of anti-HCV.

Before the improvements in infection control associated with conducting this study, the NLI Endoscopy Unit practices during UGIE appeared ideal for transmitting cross-infections. Damaged endoscopes were often used during UGIE, and reprocessing was frequently brief and inadequate, particularly at times when many UGIE were being performed. The chances of cross-infections could be exacerbated, because air and water channels in most flexible endoscopes, which often retain patient matter, were not fully accessible to brushing and could remain contaminated after cleaning.¹⁴

In addition, disposable biopsy forceps were reused for more than 1 patient. Because it would be unethical to study patients by using less than the standard accepted procedures and reprocessing practices, our protocol required that the recommended reprocessing guidelines be meticulously followed during the study. The nurses who reprocessed the endoscopes and who assisted the physicians with UGIE received training before the study and were observed during the procedures. We had damaged endoscopes repaired and provided new endoscopes and sterile single-use biopsy forceps for use in the study.

Most patients undergoing UGIE, adult male Egyptian farmers, were at high risk for complications of chronic HCV infection. The patients in this group were not reliable in returning for medical care, unless they were sick, particularly to see someone involved with performing UGIE and planning to obtain blood samples. Our efforts to encourage them to return were focused upon the 249 patients who were anti-HCV negative at the time of the UGIE. Even then, we only obtained a 60% follow-up of this at-risk group, despite telephone contacts and home visits with those not returning. However, the 100 lost to follow-up did not demographically differ from the 149 in the study.

We screened for anti-HCV seroconversion by using EIA and sought to document HCV infection by detecting HCV-RNA with RT-PCR. Exposure was assessed by testing the individual previously examined with the same endoscope for HCV-RNA. Comparing sequenced viruses from both the infectious and the at-risk individuals would have confirmed HCV transmission. However, the 2 patients who were anti-HCV converters had HCV-RNA in their follow-up blood samples and also had HCV in their sample taken at the time of the UGIE. The other 2 did not convert for HCV-RNA, even though anti-HCV was detected when retesting the blood samples. One explanation for these

results is that the former 2 patients had early stage HCV infection during UGIE before anti-HCV was detectable and the latter 2 had early clearances of HCV infections. There are other possible explanations. The most likely are the following: in the first case, the initial EIA test for anti-HCV could have been a "false negative," and, in the second case, the EIA for anti-HCV could have been "false positive," or low levels of HCV-RNA may have been undetectable by our RT-PCR testing.

The background anti-HCV seroconversion rate in sex- and age-matched controls was 1% per year, which agrees with our previous reports that the majority of new infections occur in children; two thirds of those who seroconverted in the village where the controls resided were children.²⁴ During extensive cross-sectional community-based studies of risk factors for HCV infection, we reported that inhabitants of rural Egyptian villages having UGIE were more likely to have anti-HCV than age-matched controls not having the procedure.^{22,25} The odds ratio (OR) of having anti-HCV among 22 of 3999 inhabitants who gave a history of UGIE in a Nile Delta village, with an overall anti-HCV prevalence of 24%, was 1.4 (statistically nonsignificant).²² In a larger population, 6012 inhabitants of a village with 9% prevalence, the age-adjusted association of endoscopy with anti-HCV was statistically significant (OR 6.2 among those 30 years old or younger and OR 1.7 in those older than 30 years).²⁵ However, these studies cannot be used as evidence that the UGIE caused the HCV infection, because the HCV-infected individuals could have had their UGIE from a complication of HCV.

Ciancio et al²⁶ recently reported, in a multicenter progressive cohort study in Italy, that none of 912 patients who underwent gastroscopy with endoscopes previously used on HCV carriers seroconverted for anti-HCV when international infection-control guidelines were followed. Despite the difficulties that occurred during our study, the results confirmed that HCV and HBV cross-infections would be very rare events during UGIE when the endoscopes are properly reprocessed between patients, even in a situation such as ours, in which HCV-infected blood and other body tissues are ubiquitous. Our results, however, should only be applied to viruses that are easily disinfected. They do not apply to more resistant microorganisms, eg, *Mycobacterium tuberculosis* (which is covered by FDA requirements) and spore-forming bacteria.

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DISCLOSURE

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Only D. L. Lewis has any potential conflicts of interest or commercial associations. Although assigned to the University of Georgia, he was an EPA employee at the time this study was conducted and he arranged partial funding of the project from Vision Sciences, Inc, and donation of gastroscopes from Pentax Corp, and sterile single-use biopsy forceps from Microvasive Endoscopy. No other authors had any conflicts of interest.

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