Published in final edited form as:

Gastrointest Endosc. 2009 April ; 69(4): 906–910. doi:10.1016/j.gie.2008.05.015.

Multiple endoscopic biopsies in research subjects: safety results from a National Institutes of Health series

Michael D. Yao, MD,
Washington DC Medical Center

Erik C. von Rosenvinge, MD,
Univeristy of Maryland School of Medicine

Catherine Groden, RN, and
NHGRI, NIH

Peter J. Mannon, MD
University of Alabama at Birmingham

Abstract

Background—Routine endoscopic mucosal biopsies are generally considered safe. However, the outcomes of performing large numbers of biopsies in subjects enrolled in research protocols have not been reported.

Objective—Our purpose was to assess the safety of taking numerous mucosal biopsy specimens during endoscopic procedures (eg, >20/endoscopic procedure) in research subjects.

Design—Single-center retrospective chart review.

Setting—Research hospital: National Institutes of Health (NIH) Clinical Center.

Patients—Volunteers who underwent research protocol endoscopies with large numbers of biopsies during 2001 to 2008 at the NIH.

Main Outcome Measurements—Charts were reviewed for the occurrence of procedure-related major/minor complications.

Results—A total of 253 research endoscopies were performed on 133 patients: 169 colonoscopies, 64 sigmoidoscopies, and 20 upper endoscopies. A total of 9,661 biopsy specimens were obtained for research and histopathologic examination (mean 38.2 ± 15.6 per procedure). No major complications were identified. Minor complications occurred with 13 (5.1%) lower endoscopic procedures and included self-limited bleeding (4), pain (5), or both (4). There was no statistically significant association between the number of biopsies, type of procedure, location of research biopsies, operator, polypectomy, or the use of nonsteroidal anti-inflammatory drugs and the risk of complications.

Reprint requests: Michael D. Yao, MD, Mucosal Immunity Section, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Dr, Bldg 10, Room 6-3742, Bethesda, MD 20892-1804. michael.yao2@va.gov.

DISCLOSURE: All authors disclosed no financial relationships relevant to this publication.

If you want to chat with an author of this article, you may contact him at yaomic@mail.nih.gov.

Limitations—Retrospective design, modest sample size.

Conclusions—This is the first report on the safety of performing large numbers of endoscopic biopsies in research subjects. This practice is well tolerated and appears to have no more than minimal risk without appreciably increasing the risk of otherwise routine endoscopy.

The overall complication rate of GI endoscopy has been reported to be very low.[1, 2 and 3] Major complications such as serious bleeding or perforation are uncommon. Mucosal biopsy is routinely performed during endoscopy to obtain tissue for medically indicated histologic examination. Although rare, significant complications resulting from endoscopic mucosal biopsy have been documented in the literature, consisting mostly of reports of hemorrhage. The majority of these cases involve the use of electrocoagulating (“hot”) biopsy, but there are isolated reports of major hemorrhage after the use of standard (“cold”) biopsy forceps for tissue sampling.[4, 5, 6, 7 and 8]

The rate of bleeding complications resulting from endoscopic biopsy varies from 0.03% to 0.14% for upper endoscopy and 0.008% to 0.03% for colonoscopy.[7, 8, 9, 10, 11, 12, 13 and 14] These reports do not comment on any relationship between the number of biopsy specimens taken and the risk of subsequent bleeding. However, what data do exist concerning the safety of multiple specimens taken during colonoscopies come from reports of dysplasia surveillance in patients with long-standing inflammatory bowel disease, specifically ulcerative colitis. Two large-scale studies have demonstrated the safety of these procedures, reporting low complication rates. Koobatian and Choi[15] reported a median of 17 biopsy specimens per colonoscopy (range 1–37), and only one complication in 384 procedures. Rutter et al[16] reported a similar finding with a median of 8 biopsy specimens per procedure, and no complications in 2627 procedures. These observations suggest that multiple mucosal endoscopic biopsies can be performed with minimal risk, especially when medically indicated and in the setting of active disease.

In the research setting at the National Institutes of Health (NIH), endoscopies are commonly performed for the purpose of obtaining mucosal tissue for immune monitoring during experimental therapy and to study a disease’s natural history. Multiple biopsy specimens are required to isolate adequate numbers of specific gut mucosal immune cell populations from different anatomic areas for applications such as cell culture and flow cytometry. There is a paucity of published data on the safety of performing large numbers of mucosal biopsies of this nature, both related to the absolute numbers of specimens taken and limiting them to a defined area of the bowel (randomly throughout the colon versus limited to the duodenum or terminal ileum, for instance). Any procedures performed on patients for nonmedically indicated (ie, research) purposes must have acceptable risk profiles befitting the expected level of benefit. We believe the generally accepted safety of multiple endoscopic biopsy specimens during a single procedure (surveillance procedures in ulcerative colitis, for example) provided a basis for application to research procedures as well. Our objective in conducting this retrospective analysis was to document the overall complication rate of these types of research procedures completed at our institution to provide data for investigators and ethics committees as they consider research study design and informed consent issues for protocols involving endoscopic biopsy.

Methods

We performed a retrospective chart review of patients who underwent research endoscopies with large numbers of biopsy specimens taken as part of their participation in institutional review board–approved protocols at the NIH from 2001 to 2008. The procedures were performed by 2 operators: a senior clinical staff member with greater than 20 years of endoscopy experience, and the other an upper-level fellowship trainee.

In general, patients at the NIH are seen primarily for research purposes and must be enrolled in an existing research protocol to be examined and treated. The subjects' underlying diseases included Crohn's disease, ulcerative colitis, common variable immunodeficiency (CVID), HIV, Hermansky-Pudlak syndrome (HPS), autoimmune polyendocrine syndrome (APS), chronic granulomatous disease (CGD), and Castleman's disease; healthy volunteers are also included.

All procedures were performed with Olympus videoendoscopes (series CF-Q160 and CF-Q180 colonoscopes, series GIF-Q160 and GIF-Q180 gastroscopes, and series PCF-S sigmoidoscopes; Olympus America, Center Valley, Pa). Biopsy specimens were obtained with standard-size biopsy forceps. Patients with HPS, who have a known platelet aggregation defect, received 22 μg of desmopressin intravenously 30 minutes before the endoscopy procedure.

The primary end point of the study was the presence or absence of procedure-related complications, both major and minor. Major complications were defined as perforation; bleeding requiring repeat endoscopy, hospitalization or transfusion; sepsis; myocardial infarction; and death. Minor complications were defined as bleeding not meeting major criteria and postprocedural abdominal pain. Dates of research procedures were identified and then all available chart documentation subsequent to that procedure was reviewed. This included documented telephone conversations or physician, nurse practitioner, or study coordinator progress notes. If there were no documents in the chart after the procedure, it was assumed that there was no complication reported. In addition, data that were thought to possibly affect the incidence of complications such as patient demographics, number and location of biopsy specimens, operator, the use of polypectomy during the procedure, and the recent use of nonsteroidal anti-inflammatory drugs (NSAIDs) were extracted from each chart.

In general, the number of research biopsy specimens per procedure was specified by the individual protocol. The number of nonresearch histopathologic biopsy specimens taken was also often recorded on the endoscopy reports. When it was not, the pathology report was obtained to determine the total number of biopsy specimens. In cases where the pathology report stated "multiple pieces," this was counted as 2 specimens.

Statistical analysis

The Student *t* test was used to assess for significant differences between 2 groups of patients: those with an identified complication and those without. In addition, multivariate regression analysis was performed to identify possible predictors of postprocedure complications (the

dependent variable). All statistics were performed with either Prism 3.0 or GraphPad InStat 3 computer software (GraphPad Software, Inc, La Jolla, Calif).

Results

A total of 253 research endoscopies were performed on 133 patients (87 male, 46 female; mean age 39 years, range 14–73 years): 169 colonoscopies, 64 sigmoidoscopies, and 20 upper endoscopies (Table 1). Capture of complications was assessed to be adequate because the majority of procedures (85.4%) had an associated protocol-related hospitalization or documented telephone follow-up or outpatient visit within 30 days of the procedure.

A total of 9661 biopsy specimens were taken for research and histopathology purposes (Table 2). The mean number of biopsy specimens was 38.2 ± 15.6 per procedure with a range from 13 to 85 (some protocols required 25–30 specimens from the colon and ileum in addition to those obtained for histopathologic study). When biopsies were performed, the mean number of research biopsy specimens per segment was 24.1 (±1.9) duodenal, 28.6 (±4.2) terminal ileal, 26.0 (±3.4) pancolonic, and 25.1 (±5.1) rectosigmoid.

No major complications were identified (Table 3). Minor complications occurred with 13 lower endoscopic procedures (5.1%) and included bleeding (4), pain (5), or both (4). Chart notations of minor bleeding episodes included the descriptive terms “hematochezia,” “bright red blood per rectum,” or “blood in the stool” and were all observed 1 to 4 days after the procedure. Chart notations of pain included the descriptive terms “abdominal pain,” “abdominal cramping,” “abdominal tenderness,” or “gas pain” that all resolved without intervention and lasted no more than 4 days after the procedure. One HIV-positive patient did have postprocedure pain and fever approximately 4 hours after an ileocolonoscopy. Serial radiographs and a CT scan did not reveal the presence of a perforation. The patient’s fever and pain resolved, but his preplanned hospital stay was extended for observation. This was not included as a major complication because hospitalization itself was not a preidentified criterion.

When the procedures were stratified for the presence of minor complications (n = 13), there was no significant difference in mean age or total number of biopsy specimens taken between these 2 groups. When the procedures were stratified according to the presence of minor bleeding (n = 8) versus no bleeding (n = 245), again there was no significant difference in the total number of biopsy specimens taken between groups.

Multivariate regression analysis did not reveal any significant correlation between the underlying disease, type of procedure, location of biopsy specimens, operator, use of polypectomy, or recent NSAID use and the rate of minor complications.

Discussion

The practice of mucosal biopsy by endoscope is widely accepted and firmly established as safe and indispensable for routine diagnostic purposes. These current results demonstrate that performing large numbers of mucosal biopsies during research endoscopies carries a low risk of complications. This is the first report on the safety of performing large numbers

of endoscopic biopsies for the primary purpose of research. These data also support the conclusion that larger numbers of biopsy specimens are not associated with higher rates of complications even in subjects with active inflammatory bowel disease, immunodeficiency states, and predispositions to bleeding diatheses.

We did identify minor complications, which were characterized as abdominal pain and minor hematochezia, after the performance of 13 lower endoscopic procedures. Although 5.1% may seem to be a high complication rate, many large-scale studies on endoscopy complications do not include these categories as one of their outcomes. In the few studies that do report these outcomes, complication rates have ranged from 0.8% to 5.4% for abdominal pain and 0.22% to 2.1% for rectal bleeding.[2, 17 and 18]

The exact etiology of these minor complications is unclear. Increasing the number of biopsy specimens taken or limiting the majority of biopsies in the rectosigmoid (during a flexible sigmoidoscopy) did not seem to increase the risk of postendoscopy hematochezia. Crampy abdominal pain is a known discomfort of colonoscopy even without biopsy and it is unclear whether this symptom is related specifically to the biopsy procedure or the manipulation of the endoscope and subsequent effects of insufflation. Abdominal pain could be associated with a prolonged procedure time (to accommodate biopsy specimen retrieval) and thus increased insufflation, but these data were not studied in this report.

The significance of these defined minor complications has been raised before.[19] Although minor complications may not have serious medical sequelae, it has been questioned whether these should be more closely followed because they can lead to an overall decrease in patient satisfaction and therefore possibly cause the avoidance of future procedures.[19] This question will need further study before the full implications of minor complications can be known in both medically indicated and research settings. Although this current study is retrospective, we are confident that the majority of procedure-related complications were captured because most patients were followed up closely after endoscopy with either a preset protocol-related hospitalization, a follow-up phone call within 1 week, or an outpatient visit within 30 days. In addition, all patients were routinely provided with phone numbers of the endoscopy laboratory and had a dedicated research nurse to contact in the event of a complication. We found no difference in the rates of complications in patients who had direct observation in the hospital and those who were discharged home the same day.

In conclusion, taking numerous mucosal biopsy specimens during research endoscopies is safe, well tolerated, and does not appear to add appreciable risk to the procedure. In our series, when complications occurred they were minor and self-limited. These data should assist investigators and ethics committee members in risk assessments and informed consent issues when considering protocols using multiple endoscopic biopsy procedures.

Acknowledgments

Funded by the Division of Intramural Research, National Institute of Allergy and Infectious Disease, National Institutes of Health.

Abbreviation

APS	autoimmune polyendocrine syndrome
CGD	chronic granulomatous disease
CVID	common variable immunodeficiency
HPS	Hermansky-Pudlak syndrome
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drug

References

1. Rathgaber S, Wick T. Colonoscopy completion and complication rates in a community gastroenterology practice. Gastrointest Endosc. 2006; 64:556–562. [PubMed: 16996349]
2. Nelson D, McQuaid K, Bond J, et al. Procedural success and complications of large-scale screening colonoscopy. Gastrointest Endosc. 2002; 55:307–314. [PubMed: 11868001]
3. Waye J, Lewis B, Yessayan S. Colonoscopy: a prospective report of complications. J Clin Gastroenterol. 1992; 15:347–351. [PubMed: 1294644]
4. Eckardt V, Gaedertz C, Eidner C. Colonic perforation with endoscopic biopsy. Gastrointest Endosc. 1997; 46:560–562. [PubMed: 9434229]
5. Jiménez-Perez F, Echarri A, Jiménez E, et al. Colonic hemorrhage after standard biopsy. Am J Gastroenterol. 1994; 89:1123–1124. [PubMed: 8017387]
6. Raijman I, Sellin J, Glombicki A. Gastrointestinal bleeding after cold biopsy. Gastrointest Endosc. 1992; 38:636. [PubMed: 1397936]
7. Vu C, Korman M, Bejer I, Davis S. Gastrointestinal bleeding after cold biopsy. Am J Gastroenterol. 1998; 93:1141–1143. [PubMed: 9672346]
8. Dyer W, Quigley E, Noel S, et al. Major colonic hemorrhage following electrocoagulating (hot) biopsy of diminutive colonic polyps: relationship to colonic location and low-dose aspirin therapy. Gastrointest Endosc. 1991; 37:361–364. [PubMed: 2070990]
9. Reiertsen O, Skjøtø J, Jacobsen C, et al. Complications of fiberoptic gastrointestinal endoscopy—five years' experience in a central hospital. Endoscopy. 1987; 19:1–6. [PubMed: 3493897]
10. Quine M, Bell G, McCloy R, et al. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. Gut. 1995; 36:462–467. [PubMed: 7698711]
11. Rogers B, Silvis S, Nebel O, et al. Complications of flexible fiberoptic colonoscopy and polypectomy. Gastrointest Endosc. 1975; 22:73–77. [PubMed: 1081461]
12. Silvis S, Nebel O, Rogers G, et al. Endoscopic complications: results of the 1974 American Society for Gastrointestinal Endoscopy Survey. JAMA. 1976; 235:928–930. [PubMed: 128642]
13. Rodney W, Hocutt JJ, Coleman W, et al. Esophagogastroduodenoscopy by family physicians: a national multisite study of 717 procedures. J Am Board Fam Pract. 1990; 3:73–79. [PubMed: 2185609]
14. Gilbert D, Silverstein F, Tedesco F. National ASGE survey on upper gastrointestinal bleeding: complications of endoscopy. Dig Dis Sci. 1981; 26:S55–S59.
15. Koobatian G, Choi P. Safety of surveillance colonoscopy in long-standing ulcerative colitis. Am J Gastroenterol. 1994; 89:1472–1475. [PubMed: 8079922]
16. Rutter M, Saunders B, Wilkinson K, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology. 2006; 130:1030–1038. [PubMed: 16618396]
17. Levin T, Zhao W, Conell C, et al. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med. 2006; 145:880–886. [PubMed: 17179057]

18. Zubarik R, Fleischer D, Mastropietro C, et al. Prospective analysis of complications 30 days after outpatient colonoscopy. Gastrointest Endosc. 1999; 50:322–328. [PubMed: 10462650]

19. Harewood G. From major to minor: are all endoscopic complications created equal? Gastrointest Endosc. 2003; 57:141–143. [PubMed: 12518159]

What is already known of this topic

- Routine endoscopic mucosal biopsies are generally considered safe with very low complication rates.
- The risks of performing large numbers of biopsies (eg, >20/endoscopic procedure) have not been reported either for medically indicated or research purposes.

What this study adds to our knowledge

- In a single-center retrospective review of 253 research endoscopies with a mean of 38.2 ± 15.6 biopsies per procedure, there were no major complications identified.
- Performing numerous mucosal biopsies appears to be safe, well-tolerated, and does not appreciably increase the risk of research endoscopies.

Table 1

Patient demographics per study procedure

	No./total (%)
Procedure	
Colonoscopy	169/253 (66.7)
Sigmoidoscopy	64/253 (25.3)
Upper endoscopy	20/253 (7.9)
Sex	
Male	161/253 (63.6)
Female	92/253 (36.4)
Underlying disease	
HIV	66/253 (26.1)
Crohn's disease	65/253 (25.7)
Ulcerative colitis	52/253 (20.6)
CVID	35/253 (13.8)
Healthy volunteer	13/253 (5.1)
HPS	12/253 (4.7)
APS	7/253 (2.8)
CGD	2/253 (0.8)
Castleman's disease	1/253 (0.4)
Follow-up	
Protocol-related hospitalization	90/253 (35.6)
Telephone follow-up	63/253 (25.0)
Outpatient visit within 30 d	118/253 (46.6)
Any of the above	216/253 (85.4)
Use of NSAIDS	16/253 (6.3)
Polypectomy during research endoscopy	24/253 (9.5)

Table 2

Number and location of biopsies

Research biopsies (no./total [%])	7836/9661 (81.1)
Histopathology biopsies (no./total [%])	1825/9661 (18.9)
Mean number of biopsy specimens per procedure (no. [SD])	38.2 (15.6)
Mean number of research biopsy specimens per segment (when performed) (no. [SD])	
Duodenum	24.1 (1.9)
Ileum	28.6 (4.2)
Pancolonic	26.0 (3.4)
Rectosigmoid	25.1 (5.1)

Table 3

Complications per procedure

	No./total (%)
Perforation	0/253 (0)
Bleeding	8/253 (3.2)
Requiring hospitalization	0/8 (0)
Requiring transfusion	0/8 (0)
Requiring repeat procedure	0/8 (0)
Sepsis	0/253 (0)
Myocardial infarction	0/253 (0)
Death	0/253 (0)
Pain	9/253 (3.6)