Adenoma Detection Rate With a New Pediatric Colonoscope With a Short Turn Radius (Pentax Retroview) Compared With a Standard Pentax Pediatric Colonoscope

Date of Document: 6/13/2014

Adenoma detection rate with a new pediatric colonoscope with a short turn radius (Pentax Retroview) compared with a standard Pentax pediatric colonoscope.

Norman S. Nishioka, MD
Principal Investigator

I. BACKGROUND AND SIGNIFICANCE

Colonoscopy is widely thought to be the best screening test for detection of colorectal polyps and cancers. However, colonoscopy is not a perfect test and 6-11% of large polyps and higher numbers of smaller polyps may be missed during routine colonoscopy. The colon is a tube like organ but has many folds, and some polyps may be located proximal to (behind) these folds. One of the reasons polyps may be missed at colonoscopy is that a standard colonoscope cannot easily look behind colonic folds. The purpose of the study is to evaluate whether a new colonoscope that can easily bend to look behind these folds can detect more polyps than a standard colonoscope. As colorectal cancer is the second most common cause of cancer related mortality in the United States with over 50,000 deaths reported annually, the impact of such new knowledge would be highly significant. One of the reasons for the development of these interval colon cancers is polyps missed at colonoscopy. Polyps that are located on the proximal side of haustral folds or flexures can be difficult to detect using a conventional forward-viewing colonoscope and may contribute to adenoma miss rates. It is plausible to hypothesize that the inability to efficiently look behind colonic folds may therefore contribute to the development of interval colon cancers. An improved colonoscope that finds more precancerous and cancerous lesions could potentially protect more patients from colon cancer and decrease interval cancer rates.

Colorectal Cancer in the United States

Of cancers that affect both men and women, colorectal cancer is the second leading cause of cancer death in the United States. In 2006, 139,000 patients were newly diagnosed with colorectal cancer, and 53,000 patients died from it. Colorectal cancer is thought to develop from precancerous polyps.

Colorectal Cancer Screening, Adenoma Miss Rates and Interval Cancers

The current standard of care to prevent colorectal cancer includes colonoscopy with removal of adenomatous polyps of the colon and rectum. There is evidence that screening with colonoscopy and removal of polyps decreases the incidence of colorectal cancer compared to reference populations that are not screened. Though colonoscopy is an important method to detect precancerous polyps, it is not perfect. Tandem colonoscopy studies (where patients undergo two colonoscopies, the second performed immediately following the first) indicate a >20% miss rate for adenomatous polyps at the first colonoscopy, even when the procedure is performed by skilled endoscopists. It is known that in patients who have a normal colonoscopy, a small number will develop 'interval' colorectal cancer prior to the next planned surveillance colonoscopy. In one study of patients with colorectal cancer, 5% had a reportedly normal colonoscopy in the three years prior to diagnosis.

One of the reasons for the development of these interval colon cancers is polyps missed at colonoscopy. Polyps that are located on the proximal side of haustral folds or flexures

can be difficult to detect using a conventional forward-viewing colonoscope and may contribute to adenoma miss rates. It is plausible to hypothesize that the inability to efficiently look behind colonic folds may therefore contribute to the development of interval colon cancers.

Colonoscopes that Offer a Retrograde View:
Recently, devices that allow visualization behind haustral folds with a retrograde view have been developed with the objective to discover lesions missed by conventional endoscopy. One such device is the Third Eye Retroscope, a retrograde viewing device that is advanced through the accessory channel of the endoscope. This device provides a simultaneous anterograde and retrograde view of the colon as the colonoscope is withdrawn. In a multi-center study utilizing this device 448 patients underwent two colonoscopies, once with the colonoscope plus the Third Eye and once by standard colonoscopy. The order was randomized. The second look by Third Eye colonoscope found more additional adenomas (46% more) than a second look by standard colonoscope (20% more). This suggests that the benefit of the Third Eye Retroscope exceeds the benefit of a second look endoscopy by a standard colonoscope.

Performance and Retroflexion Properties of Colonoscopes
In contrast to a retrograde viewing device that is passed through the colonoscope's accessory device, another option for allowing a retrograde view is a colonoscope whose tip is able to bend with a shorter turning radius than a traditional colonoscope. Current colonoscopes have a longer bending radius at the tip of the instrument which makes bending the tip backwards (retroflexion)to visualize the proximal aspect of colonic folds difficult.

Kessler et al. showed that a prototype pediatric colonoscope with a short bending section at the tip was able to successfully retroflex at the cecum more often compared to one with a standard bending section, without compromising the ability to reach the cecum or need to change patient position.

We plan to study a new pediatric colonoscope (Pentax Retroview) which has a short turning radius and can easily retroflex within the colon to provide both an anterograde and retrograde view, though not simultaneously. Pediatric colonoscopes are widely used for adult colonoscopy, and are more flexible than adult colonoscopes. We have studied the new colonoscope in anatomic bench models, and it led to higher detection rates of simulated polyps, especially those found behind folds. This study will compare the detection of precancerous and cancerous lesions utilizing the new colonoscope to that of a standard pediatric colonoscope with a standard bending section. We will measure the number of precancerous and cancerous lesions found at the colonoscopy.

References
Colorectal (Colon) Cancer. Centers for Disease Control and Prevention. 6 Jul 2010.
Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, et al. Prevention of colorectal cancer by colonoscopy polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993 Dec 30; 329(27):1977-81.

Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology. 1997 Jan; 112(1):24-28.

Rex DK, Rahmani EY, Haseman JH, et al. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterology 1997; 112: 17-23.

Baxter N, Goldwasser M, Paszat L, Saskin R, Urbach D, Rabeneck L. Association of Colonoscopy and Death Rates from Colorectal Cancer. Annals of Internal Medicine. 2009 Jan; 1250(1): 1-8.

Demarco DC, Odstreil E, et al. Impact of experience with a retrograde-viewing device on adenoma detection rates and withdrawal times during colonoscopy : the Third Eye Retroscope study group. Gastrointestinal Endoscopy. 2010 Mar; 71(3): 542-5

Kessler WR, Rex DK. Impact of bending section length on insertion and retroflexion properties of pediatric and adult colonoscopes. Am J Gastroenterology. 2005 Jun; 100 (6):1290-5.

Waye JD, Heigh, JH et al. A retrograde viewing device improves detection of adenoma in the colon: a prospective efficacy evaluation (with videos). Gastrointestinal Endoscopy. 2010 Mar; 71(3):551-6.

II. SPECIFIC AIMS

Objective: We would like to learn whether the new colonoscope that provides both a traditional and a retrograde view (bending 180 degrees to look behind itself) of the colon can detect more polyps than a standard colonoscope that only provides a forward-facing view. We wish to effectively demonstrate the utility of the new colonoscope (Pentax Retroview Colonoscope) as the objective of this study is to determine polyp (adenoma) detection rates in human subjects undergoing colonoscopy for polyp surveillance.

III. SUBJECT SELECTION

Subjects will be recruited from patients already referred to the physician investigators for surveillance due to personal history of colon polyps found during colonoscopy done 3 or more years previously. This will allow for evaluation of the colonoscope in a population that requires surveillance colonoscopy. The physician investigators have a sufficiently large referral base for surveillance colonoscopy that will allow recruitment for this number of participants. The participants will be undergoing a colonoscopy by attending endoscopists, regardless of whether they enroll in the study or not.

This is a multi-site study.

IV. SUBJECT ENROLLMENT

For those randomized to the new colonoscope, the colonoscope will provide a forward-facing view of the colon during advancement to the cecum (standard of care). The scope will then be withdrawn all the way to the rectum and the colon will be inspected using the forward-facing view (standard of care). The colonoscope will then be re advanced to the cecum and be withdrawn using the retrograde view.

For those randomized to the control arm, colonoscopy will be performed with a conventional colonoscope. During withdrawal in the control group, the colon will be inspected using the forward-facing view (standard of care). The colonoscope will then be re-advanced to the cecum and again withdrawn using the forward-facing view.

Patients will be randomized equally to either the new colonoscope (Pentax Retroview) or the control arm with a standard pediatric colonoscope. A total of 300 subjects will be enrolled.

V. STUDY PROCEDURES

1. Patients with prior history of colon polyps (adenomas) are referred for surveillance colonoscopy (standard of care) due to personal history of colon polyps found during colonoscopy done 3 or more years previously
2. The patients will undergo standard bowel preparation for colonoscopy (standard of care)
3. Patients will be asked during routine pre-procedure examination for colonoscopy if they are interested in participating in the study
3. Following consent, patients will be randomized to colonoscopy with either the new colonoscope or conventional colonoscope.
4. Patients will undergo colonoscopy (standard of care). All colonoscopies will be performed by a GI attending.

For those randomized to the new colonoscope, the colonoscope will provide a forward-facing view of the colon during advancement to the cecum (standard of care). The scope will then be withdrawn all the way to the rectum and the colon will be inspected using the forward-facing view (standard of care). The colonoscope will then be re advanced to the cecum and be withdrawn using the retrograde view. In subjects that are randomized to the Retroview scope, the scope is advanced to cecum and then withdrawn to rectum in forward position. The subject is reintubated. At the cecum, scope is retroflexed and withdrawn till before hepatic flexure. Then straightened out, pulled through flexure and retroflexed again. The scope is withdrawn through transverse in retroflexed view until the rectum. There has been a 50 subject trial in which the withdrawal time was recorded and an additional 9.8 minutes were added to the total withdrawal time. It is unknown if there is additional risk in the retroflexed view.

For those randomized to the control arm, colonoscopy will be performed with a conventional colonoscope. During withdrawal in the control group, the colon will be inspected using the forward-facing view (standard of care). The colonoscope will then be re-advanced to the cecum and again withdrawn using the forward-facing view.

During colonoscopy, any polyps that are found will be removed and any cancers noted will be biopsied (standard of care). 300 patients will be recruited at each site (Stanford and MGH), and the number of precancerous lesions (polyps) and cancers found at colonoscopy utilizing the two different colonoscopes will be evaluated. The adenoma detection rate (ADR), the adenoma per colonoscopy (APC) rate and the adenoma miss rate (AMR) at first pass for the two colonoscopes will be calculated.

The major endpoints are number of precancerous or cancerous lesions found during colonoscopy. We do not plan to terminate the study before enrollment has been met. The study will be terminated at the enrollment of 300 participants at each of the two sites.

6. Data sources will include procedure report, patient's electronic medical record, pathology reports and demographic information. These will be recorded in a confidential manner with PHI de-identified.

Inclusion Criteria:
1. Ability to provide informed consent
2. Adult men and women age 40 years old or older
3. Colonoscopy patients with a history of adenomatous colorectal polyps and are returning for a follow up colonoscopy 3 yrs or more after their previous procedure
Exclusion Criteria:
1. Poor or fair bowel preparation
2. Difficult first insertion of colonoscope
3. Conserved status
4. Familial polyposis
5. Inflammatory bowel disease
6. Pregnancy
7. Active GI bleeding
8. Prior colonic or rectal resection (colon not intact)
9. Screening colonoscopy
10. Colonoscopy done to evaluate symptoms like abdominal pain, diarrhea, constipation, change in bowel habit.

VI. BIOSTATISTICAL ANALYSIS

The primary endpoint is the adenoma detection rate (ADR) for the control and Retroview group. The ADR is the percentage of patients with at least one adenoma. The numbers will be compared using standard statistical analysis of proportions (e.g., http://www.ltcconline.net/greenl/courses/201/estimation/ciprop.htm). Both groups will be assumed to be normally distributed. Secondary endpoints will be the ADR for each pass of the colonoscope (i.e., the incremental adenoma pick-up rate), the overall polyp detection rate (adenomas and non-adenomas) and the mean number of adenomas identified per patient with polyps. We hypothesize that the Retroview colonoscope will detect additional adenomas at a rate of 30% compared to the a rate of 20% when using a

conventional colonoscope. Assuming a significance level of 5% and a power level of 80%, 294 patients in each arm (total of 588 patients) would be required to demonstrate this improved performance.

VII. RISKS AND DISCOMFORTS

The risk of perforation of the colon during screening/surveillance colonoscopy with polypectomy is 1:1000. There is risk of bleeding following polypectomy, but bleeding is readily fixable. These risks would apply to the patients regardless of whether they choose to participate in the study or not. It is not anticipated that participation in this study will directly pose any psychological risks to the patient.

VIII. POTENTIAL BENEFITS

The potential benefits to study subjects will be an improved colonoscopy with fewer missed precancerous (polyps) and cancerous lesions. In addition, both arms of the study will benefit by a more thorough examination of the colon (second look colonoscopy), as data from numerous studies confirms that a second look increases the number of precancerous polyps that are detected at colonoscopy. Identification of an improved colonoscope may aid future patients who undergo screening and surveillance colonoscopy in order to prevent colorectal cancer.

IX. MONITORING AND QUALITY ASSURANCE

This study will be closely monitored by Dr. James Richter, Director of Quality Assurance for the MGH GI Unit and Dr. Nishioka, the Principal Investigator of this study. Dr. Richter oversees Quality Assurance for all gastrointestinal endoscopic procedures and Dr. Nishioka as the Principal Investigator of this trial, will be responsible for ensuring that the study is conducted according to the IRB-approved protocol and regulations, and for protecting the rights, safety and welfare of the subjects. Dr. Nishioka or another physician investigator will be responsible for obtaining informed consent from study participants. Dr. Nishioka will be responsible for reporting any adverse events to the IRB. In accordance with Partners Human Research Committee (PHRC) guidelines, adverse events will be reported to the PHRC along with appropriate forms within the required time frame. Dr Nishioka is the principal investigator of this study and is directly responsible for the conduct of the study.

This is a two site study. When 100 subjects have been enrolled at a site, de-identified study data will be jointly reviewed by the lead investigators at the two sites. Any serious adverse event will be reviewed by the two lead investigators within 48 hours. The two lead investigators will be responsible for determining whether the research should be altered or stopped.

X. REFERENCES

Embedded within the body of this document.