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Retrospective Study

Obtaining research biopsies during pediatric colonoscopy: Safety and adverse events

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Abstract

AIM: To investigate the safety profile of acquiring additional intestinal biopsies for research purposes in children undergoing a medically indicated colonoscopy.

METHODS: A retrospective review of 122 pediatric patients who underwent colonoscopy over a 9 mo time period was completed. 38/122 participants consented to a research study in which 4 additional biopsies were obtained, in addition to routine biopsies. The outcomes after colonoscopy were measured in the research participants, and compared to 84 control participants who did not consent for the study. Groups were compared with regard to number of biopsies obtained, underlying diagnosis, and both serious and minor adverse outcomes. Data was collected including: age, gender, race, indication, diagnosis, number of biopsies obtained per case and post procedure adverse events. Medical records were reviewed and a questionnaire was completed by each of the ten gastroenterologists who performed procedures during the study. Physicians were asked about individual patient outcomes to ensure that all adverse events, such as perforation, excessive bleeding, infection, and minor gastrointestinal outcomes, were captured and included.

RESULTS: The research group had more biopsies obtained (mean = 13.58 ± 4.21) compared to controls (mean = 9.33 ± 4.40), $P \leq 0.0001$, however there was no difference in adverse events. Serious outcomes, defined as perforation, bleeding and infection, did not occur, in either group. As such, the relationship between serious adverse events and number of biopsies obtained was not determined. Minor gastrointestinal outcomes, such as abdominal pain, diarrhea or vomiting, were reported in 21 patients (8 research participants and 13 control participants) however the incidence of minor gastrointestinal outcomes between the two groups did not vary significantly, $P = 0.45$. Additionally, the mean

number of biopsies obtained in patients who had a minor outcome (mean = 12.1 ± 0.77), compared to those with no adverse outcome (mean = 10.34 ± 0.5), revealed no statistical difference between the groups ($P = 0.12$), suggesting that number of biopsies is not associated with incidence of minor adverse events.

CONCLUSION: Patients participating in research requiring acquisition of additional biopsies for research purposes alone, are not at an increased risk of adverse outcomes.

Key words: Pediatric colonoscopy; Outcomes; Research; Safety; Intestinal biopsy

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Core tip: Acquiring biopsies for research purposes during a colonoscopy may facilitate translational research in the field of gastroenterology. However, the safety profile of acquiring research biopsies has not been established. Our study is the first to conclude that acquiring additional biopsies for research during a colonoscopy does not pose additional risk to the pediatric patient. This manuscript may serve as a reference to researchers applying for IRB approval in biological specimen studies. Additionally, our study is additive to the body of literature on outcomes after pediatric colonoscopy, in that minor gastrointestinal symptoms were the only reported adverse event after colonoscopy.

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INTRODUCTION

Colonoscopy with biopsies is a common procedure in children for the evaluation and diagnosis of gastrointestinal disease. Serious complications, such as perforation and bleeding are routinely discussed during the consent process, however, these events are rare^[1-3]. Several adult studies have sought to measure the incidence of adverse outcomes during routine procedures^[2,4,5], and this data has largely been applied to the pediatric population^[6]. In adults, colorectal perforation is presumed to occur in 0.09% of the general population^[7,8], while it remains unclear as to whether patients with pre-existing inflammatory bowel disease (IBD) are at an increased risk for serious outcomes, such as perforation^[7,9,10]. The incidence of bleeding after colonoscopy is thought to occur infrequently during routine procedures^[8].

There is limited data on serious adverse events in children, such as bleeding. Although one study found that 38.6% (34/86) of all reported complications were

related to gastrointestinal bleeding, bleeding was not defined^[3]. Other pediatric studies did not include bleeding in their outcome analysis^[6]. Infection, similarly regarded as a serious and uncommon outcome after colonoscopy, has not been widely studied in pediatrics^[11]. Likewise, minor post-procedure gastrointestinal symptoms, such as bloating and abdominal pain, are not well described in the pediatric literature^[12].

The current pediatric studies are limited in number and do not quantify the number of routine biopsies obtained per procedure which may be a risk factor for adverse events. Additionally, these studies have not addressed whether obtaining additional biopsies solely for research purposes imposes additional risk to the patient. To our knowledge, this issue has not been addressed in the pediatric or adult literature. It is critical to establish the safety profile of collecting additional biopsies for research during routine procedures, so that investigators seeking institutional review board (IRB) approval are able to proceed with important research questions. The absence of this risk assessment may explain why studies involving the collection of pediatric biological specimens are difficult to pursue. Such IRB protocols pose a challenge to both author and reviewer, in that the lack of prior safety data serves as an obstacle for IRB approval. To address this gap, we performed a retrospective review for all children undergoing routine medically indicated colonoscopies and measured adverse events. Thirty-one percent of the participants had previously consented for a research study involving the acquisition of four additional intestinal biopsies designated for research purposes. By comparing adverse events in the research study participants to patients who did not consent, the controls, we established that acquiring additional biopsies for research alone is safe.

MATERIALS AND METHODS

We performed a retrospective review of all pediatric patients undergoing a medically indicated routine colonoscopy from June 5, 2013-March 5, 2014. Anesthesia was provided by pediatric anesthesiologists.

Patients who had previously provided written and oral consent for a biological specimens study were identified ($n = 38$); these participants consented to have four additional intestinal biopsies taken for research purposes alone. This research-consented cohort was then compared to non-study participants ($n = 84$), who had only routine biopsies obtained during the procedure.

Data was collected including: age, gender, race, indication, diagnosis, number of biopsies obtained per case and post procedure adverse events. Post-procedure adverse events were defined as events occurring within one week of the procedure. Medical records were reviewed for patient phone calls, general practitioner and gastroenterology clinic appointments, emergency department visits and hospital admissions within one week post-procedure. For those patients who were admitted to the hospital prior to their colonoscopy, the

Table 1 Participant demographics

	Research group (n = 38)	Control group (n = 84)	P value ¹
Sex			
Male, n (%)	20 (52.6)	48 (57.1)	0.64
Female, n (%)	18 (47.4)	36 (42.9)	
Age in years, n (%)			
0-5	1 (2.6)	16 (19.0)	0.05
6-12	10 (26.3)	19 (22.6)	
13-21	27 (71.1)	49 (58.3)	
Race			
White, n (%)	5 (13.2)	26 (31)	0.04
Non-white, n (%)	33 (86.8)	58 (69)	
Diagnosis			
IBD ² , n (%)	17 (44.7)	21 (25)	0.03
Normal histology, n (%)	21 (55.3)	63 (75)	
IBD diagnosis			
CD ³ , n (%)	11 (28.9)	10 (11.9)	0.23
UC ⁴ , n (%)	5 (13.2)	11 (13)	
IC ⁵ , n (%)	1 (2.6)	0	
History of IBD			
Yes	8	12	0.54
No	9	9	

¹All P values calculated to significance level of 0.05, ²Inflammatory Bowel Disease, ³Crohn's disease, ⁴Ulcerative colitis, ⁵Indeterminate colitis.

inpatient record was reviewed.

We administered a questionnaire to the ten gastroenterologists who performed procedures during the aforementioned time period regarding individual patient outcomes to ensure that all adverse events, such as perforation, excessive bleeding, infection, and minor gastrointestinal outcomes, were captured and included. This study was approved by the Office of the Human Research Protection Program, Institutional Review Board at Albert Einstein College of Medicine, Bronx, NY.

Statistical analysis

Differences in participant demographics between groups were compared using analysis of variance or *t* tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. All analyses were performed using GraphPad Prism version 6 (San Diego, CA). All tests for significance were two-sided, and a value of $P < 0.05$ was considered significant.

RESULTS

A total of 122 colonoscopies were performed during the study period: 38 patients consented to have additional biopsies obtained for research during the medically indicated procedure, compared to 84 non-research related cases. One thousand two hundred and ninety biopsies were obtained, including 136 intestinal biopsies for research alone. The average number of biopsies obtained per case was significantly higher in the research cohort, 13.6 compared to 9.3 in the control group, ($P < 0.0001$) (Table 1). Participant demographics are detailed in Table 1. Of note, statistical differences in race and

Table 2 Minor gastrointestinal outcomes

	Research group (n = 38)	Control group (n = 84)	P value ¹
Gastrointestinal symptom after Procedure, n (%)			
Yes	8 (21.1)	13 (15.5)	0.45
No	30 (78.9)	71 (84.5)	
Mechanism of reporting			
Phone call	6	6	0.14
PGI ² clinic visit	0	1	
ED visit	2	1	
Inpatient	0	5	
Management			
Outpatient	5	6	0.81
Admission to hospital	1	1	
Referral to ED	2	1	
Continued admission	0	5	
Gastrointestinal symptom ³ (%)			
Abdominal pain only	2 (5.3)	4 (4.8)	0.82
Abdominal pain + diarrhea and/or vomiting	3 (7.9)	5 (6.0)	
Rectal bleeding	3 (7.9)	2 (2.4)	
Other	2 (5.3)	3 (3.6)	
Number of Biopsies			
Mean \pm SD ⁴	13.6 \pm 4.2	9.3 \pm 4.4	< 0.0001

¹All P values calculated to a significance level of 0.05, ²pediatric gastroenterology, ³In research group, 1 patient with both abdominal pain and rectal bleeding, 1 with both rectal bleeding and constipation and in control group, 1 patient with rectal bleeding and diarrhea; ⁴standard deviation.

age were observed in the research compared to the control groups, $P = 0.04$ and $P = 0.05$, respectively. One patient (2.6%), age 0-5, participated in the research study, compared to 16 (19%) who underwent routine colonoscopy alone ($P = 0.05$). No statistical difference in gender distribution was observed when comparing research to control participants.

The research cohort consisted of 38 patients, 17/38 (44.7%) of whom had IBD, compared to 21/84 (25%) of the patients in the control group ($P = 0.03$) (Table 1). IBD diagnosis type, such as Crohn's disease (CD) or ulcerative colitis (UC), did not vary significantly between the two groups, $P = 0.23$.

There were no cases of perforation, infection or hemorrhage in the research or the control group. Given that no serious outcomes occurred in our cohort, the relationship between number of biopsies and serious adverse events was not measured. Minor gastrointestinal outcomes, however, did occur in 8/38 research participants, and 13/84 control participants (Table 2). The incidence of minor gastrointestinal outcomes was not statistically different when comparing the research and control groups, $P = 0.45$, although the research group had significantly more biopsies obtained per procedure, $P < 0.0001$. Additionally, the mean number of biopsies obtained in patients who had a minor outcome (mean = 12.1 \pm 0.77), compared to those with no adverse outcome (mean = 10.34 \pm 0.5), revealed no statistical difference between the groups

Table 3 Indications for colonoscopy

Indication (%)	Research (n = 38)	Control (n = 84)	P value ¹
Abdominal pain	50	50	1
Diarrhea	44.7	36.9	0.41
Rectal bleeding	36.8	34.5	0.8
Weight loss	44.7	20.2	0.01
Loss of appetite	34.2	10.7	0.002
Constipation	18.4	15.5	0.68
Vomiting	15.8	14.3	0.83
Fatigue	23.7	3.57	0.001
Fever	7.89	3.57	0.31
Joint pain	10.5	1.19	0.02
Rash	5.26	0	0.03

¹All P values calculated to a significance level of 0.05.

($P = 0.12$), suggesting that number of biopsies is not associated with incidence of minor adverse events.

When comparing mechanism of reporting and management of adverse minor events no statistical differences were noted when comparing research participants to controls. Likewise, gastrointestinal symptoms reported as minor events were similar between the two groups.

Overall, during this time period, 38 children with IBD underwent colonoscopy: 47.4% (18/38) of this group were newly diagnosed patients, 11 with CD, 6 with UC, and 1 with indeterminate colitis, while 52.6% (20/38) had been previously diagnosed with IBD. Minor outcomes occurred in 21% (8/38) of patients with IBD. The incidence of minor adverse events in IBD versus non-IBD patients, did not vary significantly between the two groups, $P = 0.45$.

The most common indication for colonoscopy was abdominal pain, occurring in 50% of patients, while diarrhea was the second most common indication (Table 3). Weight loss, loss of appetite, fatigue, joint pain and rash occurred more often in the research group, $P = 0.01$, $P = 0.002$, $P = 0.001$, $P = 0.02$, and $P = 0.03$, respectively.

DISCUSSION

To our knowledge, no studies to date have evaluated the safety profile of taking additional intestinal biopsies for research purposes. Obtaining intestinal biopsies for research may facilitate investigations that will further our understanding of pediatric gastrointestinal illnesses. Our study shows that participation in research during a medically indicated colonoscopy does not place the patient at an increased risk for bleeding, perforation, infection, or minor gastrointestinal outcomes, which is in line with prior pediatric studies, as complications during routine colonoscopy are rare^[3,6,7,9,11,13], and can be applied to studies involving biological specimens.

Adverse events after pediatric colonoscopy, particularly in regard to IBD, have not been well studied, as subjects with pre-existing disease are often excluded from the cohort^[6]. Our data suggests that patients with IBD are not at increased risk for perforation or bleeding,

which refutes prior findings^[10]. A larger percentage of IBD patients (8/38, 21%) sustained minor adverse outcomes compared to non-IBD patients (13/84, 15.5%), however this difference was not found to be statistically significant. Our findings support a prior study by Tam *et al.*^[9] that evaluated pain indices in children with IBD, pre and post procedure, and found that patients with functional bowel disease report more pain, compared to children with IBD^[9].

Interestingly, our research-consented cohort consisted of a larger percentage of IBD patients, 44.7% compared to 23.8% in the control group. From this, we may conclude that parental concern is greater in children more likely to have IBD, which may explain a greater willingness to participate in studies or to benefit from research. Alternatively, selection bias may impact the recruitment of children most likely to have IBD. In this study, however, all children undergoing colonoscopy during the aforementioned time period were asked to participate.

Given that serious adverse events did not occur in our cohort, we were unable to correlate number of biopsies obtained with incidence of serious adverse events. However, we did observe that of the patients who reported minor gastrointestinal outcomes, most (71.4%) reported the same symptom with which they presented for colonoscopy. Therefore, minor gastrointestinal events occurring after a procedure may be secondary to the primary gastrointestinal complaint, rather than the procedure. In regard to the consent process and clinical practice, clinicians may reassure parents that minor symptoms after a procedure are most commonly related to underlying symptoms on presentation, and not to the colonoscopy itself.

There are few studies in the current pediatric literature that discuss minor adverse outcomes after colonoscopy. Our study found that 17.2% of our population reported minor symptoms after colonoscopy, which is consistent with prior data, for example, Steiner *et al.*^[12] found that post-procedure symptoms occur in 14%-17% of patients; sore throat, diarrhea and excessive gas occurred in 6% of patients, while abdominal pain occurred in 3%^[12]. In our study 1.6% of participants were admitted post procedure for observation, while Steiner *et al.* admitted 1.1% patients, suggesting that the general concern level regarding minor symptoms is low. Of the 17 patients who reported symptoms, 1 was under the age of 5, suggesting either that minor symptoms are more common in older children, or that underreporting is at play in younger age groups. On a similar note, only 1 patient between the ages 0-5 participated in the research study, compared to 16 children in the control group under the age of 5, suggesting that parents of very young children are less likely to consent for studies requiring the collection of biological specimens. In one study, children 0-5 years of age were the most likely group to have a complication, $P \leq 0.001$ ^[3]; this supports the notion that very young

patients may have an increased risk for complications after colonoscopy and that children over the age of 5 may be more suitable candidates for research studies involving acquisition of additional biopsies.

The limitations of our retrospective study include small sample size, limited duration of the study, and selection bias, as underlying gastrointestinal symptoms may have affected study outcome. Additional studies with larger groups of pediatric patients undergoing colonoscopy for medical reasons, while participating in research, are warranted in order to further attest that no additional risk is imposed to the patient. This will allow researchers to pursue questions that will enhance our current knowledge of chronic gastrointestinal problems in children, specifically IBD.

COMMENTS

Background

Colonoscopy with biopsies is a common procedure in children for the evaluation and diagnosis of gastrointestinal disease. There is limited data on serious adverse events in children, such as bleeding, infection and perforation. Likewise, minor post-procedure gastrointestinal symptoms, such as vomiting and abdominal pain, are not well described in the pediatric literature. Current pediatric studies have not addressed whether obtaining additional biopsies solely for research purposes imposes additional risk to the patient. It is critical to establish the safety profile of collecting additional biopsies for research during routine procedures, so that investigators may proceed with studies involving biological specimens. The lack of safety data may explain why studies involving the collection of pediatric biological specimens are difficult to pursue.

Research frontiers

Institutional review board (IRB) protocols involving biological specimen collection pose a challenge to both author and reviewer, in that the lack of prior safety data serves as an obstacle for IRB approval. In order to address key research questions using translational research methods, safety data must be available for reference.

Innovations and breakthroughs

To date, the incidence of adverse events occurring when collecting additional biopsies for research during medically indicated colonoscopies has not been addressed in the pediatric or adult literature.

Applications

The study results suggest that acquiring additional biopsies for research during medically indicated colonoscopies is safe.

Terminology

Serious adverse events after colonoscopy include bleeding, perforation and infection. Minor events after colonoscopy include abdominal pain, diarrhea and vomiting.

Peer-review

This is a small retrospective study in which the authors assessed the safety profile of acquiring additional intestinal biopsies for research purposes during medically indicated colonoscopies. The results indicate that it is safe to acquire such biopsies in children for the purposes of facilitating translational research.

The publication of this study may serve as a reference for researchers seeking IRB approval in biological specimen studies, and suggests the need for larger studies in the future.

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