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ABOUT COVER

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AIMS AND SCOPE

The primary aim of World Journal of Gastrointestinal Endoscopy (WJGE, World J Gastrointest Endosc) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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ORIGINAL ARTICLE

Retrospective Study Pediatric endoscopy across multiple clinical settings: Efficiency and adverse events

Erin Crawford, Ramy Sabe, Thomas J Sferra, Carolyn Apperson-Hansen, Ali S Khalili

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Abstract

BACKGROUND

Endoscopic procedures are becoming increasingly important for the diagnosis and treatment of gastrointestinal disorders during childhood, and have evolved from a more infrequent inpatient procedure in the operating room to a routine outpatient procedure conducted in multiple care settings. Demand for these procedures is rapidly increasing and thus there is a need to perform them in an efficient manner. However, there are little data comparing the efficiency of pediatric endoscopic procedures in diverse clinical environments. We hypothesized that there are significant differences in efficiency between settings.

AIM

To compare the efficiency and examine adverse effects of pediatric endoscopic procedures across three clinical settings.

METHODS

A retrospective chart review was conducted on 1623 cases of esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy performed between January 1, 2014 and May 31, 2018 by 6 experienced pediatric gastroenterologists in three different clinical settings, including a tertiary care hospital operating room, community hospital operating room, and free-standing pediatric ambulatory endoscopy center at a community hospital. The following strict guidelines were used to schedule patients at all three locations: age greater than 6 mo; American



Society of Anesthesiologists class 1 or 2; normal craniofacial anatomy; no anticipated therapeutic intervention (e.g., foreign body retrieval, stricture dilation); and, no planned or anticipated hospitalization post-procedure. Data on demographics, times, admission rates, and adverse events were collected. Endoscopist time (elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering) and patient time (elapsed time from patient registration to that patient exiting the operating room or endoscopy suite) were calculated to assess efficiency.

RESULTS

In total, 58% of the cases were performed in the tertiary care operating room. The median age of patients was 12 years and the male-to-female ratio was nearly equal across all locations. Endoscopist time at the tertiary care operating room was 12 min longer compared to the community operating room (63.3 \pm 21.5 min vs 51.4 \pm 18.9 min, P < 0.001) and 7 min longer compared to the endoscopy center (vs 56.6 \pm 19.3 min, P < 0.001). Patient time at the tertiary care operating room was 11 min longer compared to the community operating room (133.2 ± 39.9 min vs 122.3 ± 39.5 min, P < 0.001) and 9 min longer compared to the endoscopy center (vs 124.9 ± 37.9 min; P < 0.001). When comparing endoscopist and patient times for EGD and EGD/colonoscopies among the three locations, endoscopist, and patient times were again shorter in the community hospital and endoscopy center compared to the tertiary care operating room. Adverse events from procedures occurred in 0.1% (n = 2) of cases performed in the tertiary care operating room, with 2.2% (n = 35) of cases from all locations having required an unplanned admission after the endoscopy for management of a primary GI disorder.

CONCLUSION

Pediatric endoscopic procedures can be conducted more efficiently in select patients in a community operating room and endoscopy center compared to a tertiary care operating room.

Key Words: Pediatric endoscopy; Efficiency; Adverse events; Tertiary care operating room; Community operating room; Endoscopy center

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Core Tip: This was a retrospective study where we compared the efficiency of pediatric endoscopic procedures in a tertiary care operating room, community operating room, and endoscopy center and secondarily examined adverse events of procedures across these settings. We found that with using strict, identical scheduling guidelines for all locations, undergoing esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy at the community hospital room and endoscopy center was significantly faster for the patient and endoscopist when compared to the tertiary care operating room. The rate of adverse events was similar across all three locations.

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INTRODUCTION

Endoscopic procedures are crucial for the diagnosis, treatment, and surveillance of gastrointestinal disorders in children. Moreover, the demand for these services is increasing[1]. Along with the increased utilization, the clinical setting in which these procedures are performed is changing and are now being performed as outpatient procedures conducted in multiple clinical settings[1-5]. While they are most commonly performed in operating rooms within tertiary care institutions or dedicated pediatric endoscopy suites, many endoscopies are being performed in outpatient centers[3].

With the overall increasing demand for endoscopic procedures, there is a need to perform them in an efficient manner. Locations outside of pediatric tertiary care centers have the potential to accommodate a high volume of patients due to the elimination of emergent procedures and scheduling of lower risk patients. Clinical reports regarding the development of adult and pediatric endoscopy units have focused on defining metrics used to assess efficiency, ranging from productivity metrics such as the number of procedures per hour to operational metrics such as turnover time [2,6]. Several adult studies



have shown turnover time, the time between procedures, varies among clinical settings (e.g., hospitals, ambulatory surgery centers) and is the main factor contributing to delay of procedures and the primary predictor of the number performed per hour[7,8]. However, there are substantial differences in the workflow between pediatric and adult patients that limit the applicability of adult metrics to the pediatric population[9-11]. There is no universal consensus on how efficiency can be optimized in pediatrics and scant information on its application in outpatient endoscopy centers.

The main objective of our study was to evaluate the efficiency of endoscopic procedures performed by pediatric gastroenterologists in diverse clinical settings. Secondarily, we assessed adverse events associated with endoscopic procedures performed in select pediatric patients at non-tertiary care facilities.

MATERIALS AND METHODS

We conducted a retrospective chart review of patients cared for by the Division of Pediatric Gastroenterology, Hepatology & Nutrition at University Hospitals Rainbow Babies and Children's Hospital (Cleveland, OH, United States) who underwent an outpatient esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopy between January 1, 2014 and May 31, 2018. This study was approved by the local institutional review board.

Locations

During the period of this study, the Division performed endoscopies at three locations, including pediatric tertiary care hospital operating room, community hospital operating room, and a free-standing pediatric ambulatory endoscopy center at a community hospital. All locations were staffed by the same pediatric anesthesia and endoscopy personnel. The tertiary care hospital had a single dedicated operating room for inpatient and outpatient procedures; the endoscopist did not perform endoscopies outside of the assigned operating room. The anesthesiologist assigned to the endoscopy cases in the tertiary care operating room potentially covered other surgical cases occurring simultaneously in other rooms. The community hospital operating room and the community pediatric ambulatory endoscopy unit consisted of one procedure room. The rooms in these latter two settings were dedicated to the outpatient endoscopic procedures; however, different from the tertiary care hospital, each room had a pediatric anesthesiologist assigned exclusively to that location. Endoscopic procedures were scheduled back-to-back: 60 min for combined EGD and colonoscopies at all locations; 60 min for EGD at the tertiary care operating room; and, 30 min for EGD at the community hospital and endoscopy center.

Endoscopic case characteristics

During the period of this study, our institution followed strict guidelines to schedule patients at the community locations. These guidelines were developed through consensus opinion among the pediatric gastroenterologists, pediatric anesthesiologists, and endoscopy personnel. Patients were eligible for these locations if the following criteria were met: age greater than 6 mo; American Society of Anesthesiologists class 1 (healthy person) or 2 (mild systemic disease); normal craniofacial anatomy; no anticipated therapeutic intervention (e.g., foreign body retrieval, stricture dilation, control of bleeding, variceal ligation); and, no planned or anticipated hospitalization post-procedure. Additionally, urgent or emergent cases were not performed at these locations. For this analysis, we used the same criteria to select patients undergoing endoscopy at the tertiary care hospital operating room for comparison. Also, the last case of each day was excluded from analysis as we are unable to calculate the endoscopist time. Cases that preceded inpatient procedures at the tertiary care operating room also were excluded to ensure timing and scheduling of cases were as similar as possible at all three locations.

Physicians

We reviewed only those cases performed by the pediatric gastroenterologists who performed endoscopies at the tertiary care operating room and one of the other locations. These 6 pediatric gastroenterologists were board certified, experienced endoscopists.

Data collection

We extracted data for all endoscopic procedures meeting the above criteria. Fewer cases were performed at the community ambulatory endoscopy center as compared to the other locations. To control for this disparity, cases performed at that site were matched by physician with cases performed at the tertiary care operating room; the cases from the tertiary care operating room were selected chronologically at the start of a calendar year until the number of cases between the two locations were approximately equal for each of those three physicians. Patient demographics, time variables (patient registration, patient and physician entering operating room, and patient exiting operating room), procedural or anesthesia complications, unexpected admissions, and fellow participation in the procedure were extracted from the medical record.



Adverse events were defined as endoscopic complications (e.g., gastrointestinal bleeding or perforation), sedation and cardiopulmonary complications (e.g., respiratory failure, need for intubation), any cause necessitating unintended emergency department visit or hospital admission, and hospital admission for ongoing medical care. We included hospital admission for ongoing medical care as an adverse event as patients undergoing endoscopy in the community settings would require transportation to the tertiary care hospital for care (also see guidelines for scheduling above).

Endoscopist time (ET) and patient time (PT) were calculated for each case. ET was defined as elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering. PT was defined as elapsed time from patient registration to that patient exiting the operating room or endoscopy suite. These times by definition include room turnover time and provide estimates of real time for the physician and patient.

Statistical analyses

Statistical analyses were performed by a trained statistician. Descriptive statistics were generated for each of the variables collected. Categorical data are reported as frequencies and percentages and when appropriate, χ^2 analyses were used. Continuous data are reported as numbers (*n*), means and standard deviations, and medians, and when appropriate, analysis of variance and unpaired *t*-test were used for analyses. Unless otherwise stated, statistical testing was conducted using two-sided alternatives with a type I error level of 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) was used to generate the statistics.

RESULTS

We identified 1623 cases (Table 1). Just over half were performed in the tertiary care operating room. The fewest were performed in the community ambulatory endoscopy center (7.6%). All cases were performed under monitored anesthesia care using propofol. The median age of the patients was 12 years, and the male-to-female ratio was nearly equal. There were no differences in age or sex among the cases performed at each endoscopy site or by each physician. Fellows participated in 38% of cases, with the highest percentage in the tertiary care operating room.

Efficiency

We found the tertiary hospital operating room to be the least efficient site to perform endoscopy even controlling for physician, patient age, fellow participation, and type of procedure (Table 2). The ET in the tertiary hospital operating room was 11.9 min longer than in the community operating room (P < P0.001) and 6.7 min longer than in the community endoscopy center (P < 0.001). Likewise, the PT at the tertiary care operating room was 11.2 min longer than the community operating room (P < 0.001) and 8.3 min longer than the endoscopy center (P < 0.001).

We compared the ET and PT for EGD and EGD/colonoscopies between the specific locations given that differences in case mix amongst locations may have affected the results, and confirmed the community operating room and endoscopy center were more efficient for each of these types of procedures (Table 3). We further evaluated the times based on individual physicians. Compared to the times in the tertiary care operating room, all of the physicians had a shorter ET in the community operating room and endoscopy center, and 5 of the 6 physicians had a shorter PT in the community operating room and endoscopy center compared to the tertiary care operating room (Table 4). The 1 physician (physician 6 in Table 4) with the longer PT in the community operating room compared to the tertiary care operating room ($136.5 \pm 35.7 vs 135.9 \pm 41.8$), also had the longest patient and endoscopist times overall. We did not calculate the statistical significance of ET and PT between physicians because the proportions of cases across locations were not equal.

Using analysis of variance, fellow participation did not significantly affect endoscopist or patient time when considering all cases, and we found that location accounted for the affect (P < 0.001). Fellow participation in the tertiary care operating room was associated with longer PT and ET, and the presence of a fellow overall resulted in the longest times.

Adverse events

Unplanned admissions following an endoscopic procedure occurred for a small number of patients (all locations, 2.2%, n = 35). The majority of these (n = 33) were for further management of a primary GI disease (e.g., inflammatory bowel disease) and not an endoscopic or anesthesia related complication. Patients were less frequently admitted for any reason from each of the two community-based locations as compared to the tertiary operating room (community operating room, 0.2% of total at site, n = 4; community endoscopy center 0.1% of total at site, n = 1; tertiary hospital operating room, 1.8% of total at site, n = 30). Endoscopic complications occurred in two of the evaluated cases (0.1%). Both involved patients undergoing an EGD and colonoscopy in the tertiary hospital operating room. One patient was admitted to the pediatric intensive care unit for management of gastrointestinal bleeding requiring a blood transfusion and the other to the general medical unit for observation for concern of a



Table 1 Demographics, procedures, and fellow participation by location

Characteristic	Value	Value				
	Tertiary care OR	Community OR	Endoscopy center	Overall		
Age, yr (median) ¹	11	12	12	12		
Male, $n (\%)^1$	494 (52.4)	268 (48.0)	63 (51.2)	825 (50.8)		
EGD, n (%)	537 (57)	283 (50.7)	56 (45.5)	876 (54)		
EGD/colonoscopy, n (%)	405 (43)	275 (49.3)	67 (54.4)	747 (46)		
Total procedures, <i>n</i> (%)	942 (100)	558 (100)	123 (100)	1623 (100)		
Fellow participation, n (%)	499 (53)	89 (16)	25 (20)	613 (38)		

¹There were no significant differences in the distribution of age and sex across the clinical settings. EGD: Esophagogastroduodenoscopy; OR: Operating room.

Table 2 Endoscopist time and patient time in minutes by location					
	Tertiary care OR	Community OR	Endoscopy center	<i>P</i> value ¹	
ET (mean ± SD)	63.3 ± 21.5	51.4 ± 18.9	56.6 ± 19.3	< 0.001	
PT (mean ± SD)	133.2 ± 39.9	122.0 ± 39.5	124.9 ± 37.9	< 0.001	

¹ANOVA controlling for physician, patient age, fellow participation, and type of procedures. ET: Endoscopist time; OR: Operating room; PT: Patient time; SD: Standard deviation.

Table 3 Endoscopist time and patient time in minutes by location and procedure						
	Procedure	Tertiary care OR	Community OR	Endoscopy center	P value	
ET (mean ± SD)	EGD	63.2 ± 20.2	39.6 ± 13.6	45.0 ± 13.3	< 0.001	
	EGD/colonoscopy	75.6 ± 17.3	63.4 ± 16.0	66.3 ± 18.0	< 0.001	
PT (mean ± SD)	EGD	121.4 ± 39.0	107.7 ± 34.2	112.9 ± 31.8	< 0.001	
	EGD/colonoscopy	148.4 ± 36.1	137.4 ± 38.9	135.0 ± 39.5	< 0.001	

ET: Endoscopist time; OR: Operating room; PT: Patient time; SD: Standard deviation.

gastrointestinal bleed. A fellow was present during the endoscopy for one of the two complications.

DISCUSSION

The goals of our study were to assess the efficiency of pediatric endoscopic procedures in different clinical settings and to evaluate whether the performance of these procedures in a community setting was associated with an excess of adverse events. Changing indications for endoscopic procedures and a steady increase in gastrointestinal disease burden in this population resulted in an increase in demand for these procedures to which the medical community must adapt[1]. From 2011 to 2018, our institution expanded from three to nine pediatric gastroenterologists and the number of completed endoscopic procedures more than doubled. Improving efficiency without compromising safety is essential to accommodate the increased demand of endoscopic procedures and prevent delays in diagnosis and treatment.

We found it was more efficient to perform endoscopic procedures in two community-based locations compared to a tertiary care operating room. As our measures of efficiency, we used ET to measure time between cases for the endoscopist including room turn-over and other system delays and PT to include time spent at the hospital or endoscopy unit except for the time post-endoscopy in recovery. The ET was 6.7 to 11.9 min and the PT was 8.3 min to 11.2 min shorter in the endoscopy center and community operating room, respectively compared to the tertiary care operating room. The differences in ET and PT are likely due to factors specific to the tertiary care location rather than type or complexity of the case



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Table 4 Endoscopist time and patient time in min by physician						
Endoscopist time		Patient time				
Physician	Tertiary care OR	Community OR	Endoscopy center	Tertiary care OR	Community OR	Endoscopy center
1	61.9 ± 23.1	53.2 ± 20.2		131.1 ± 38.3	126.7 ± 44.9	
2	63.9 ± 17.4	45.5 ± 14.5		142.9 ± 38.9	120.8 ± 34.9	
3	63.4 ± 22.4	45.5 ± 14.5		128.3 ± 42.4	110.2 ± 31.1	
4	64.4 ± 19.1		47.8 ± 13.5	126.0 ± 36.7		113.6 ± 38.4
5	63.4 ± 16.9		59.3 ± 19.5	160.8 ± 28.8		128.0 ± 33.7
6	68.6 ± 22.5		65.4 ± 20.7	135.9 ± 41.8		136.5 ± 35.7

Data are presented as mean ± SD. OR: Operating room.

as we controlled for these variables. If we did not employ the same criteria used to schedule patients in the community locations to select the comparator patients at the tertiary care operating room, the times in the tertiary care operating room would be longer as emergent and complex cases (e.g., variceal banding, multiple comorbidities) would be included and likely result in delays.

Several studies have described factors that can impact efficiency of endoscopic procedures[7,8,12,13]. These may be related to the patient (e.g., late to registration or no-show), physician (e.g., late to procedure), or support personnel (e.g., room turnover time). While we did not directly determine causes of the differences in efficacy besides fellow participation, our results support previous findings that decreases in efficiency at the tertiary care center are less likely to be solely related to patient or endoscopist behavior as ET and PT were almost always individually faster at the community locations. However, the endoscopist's efficiency may become a limiting factor after a certain point. For example, physician 6 had comparatively longer ET and PT times at the tertiary care center and at the endoscopy center and these were the longest times overall. This may explain why the community OR had lower ET and PT times compared to the endoscopy center, although both community locations were still more efficient when compared to the tertiary care center. Overall, the loss in efficiency may be a system problem, where possible location specific factors include room turnover, availability of anesthesiology staff, or endoscopist delayed with other tasks. Trainee participation has been shown to adversely impact efficiency by prolonging procedures[8]. In our study, while fellow participation did not affect efficiency when considering all cases included, their participation specifically in the tertiary care operating room was associated with longer ET and PT. This might be due to our institution's practice of only having senior fellows participate in endoscopy sessions at the community sites. First year fellows participate in endoscopies at the tertiary care operating room.

Regarding anesthesiologist participation during endoscopic procedures, they are often being shared with other operating rooms at the tertiary care center, which may delay procedural start time. Having a dedicated anesthesiologist at the community locations eliminates this problem. It is important to note, monitored anesthesia care with propofol was used in all of the patients in this study and has been shown to be safe and efficient due to its rapid sedation and recovery time[14,15]. Thus, our data may not translate to centers using agents other than propofol or have non-anesthesiologist staff perform sedation.

Practically, the accumulated saved time at the community locations on a typical 8-h day could reach 90 min allowing for at least two additional cases per day. Adjustments to scheduling and allotted time for procedures may help meet the increasing demand by allowing more procedures to be performed in a day. Other direct benefits from performing endoscopic procedures more efficiently are increases in patient satisfaction and institutional revenue. Performing a given number of procedures within a shorter time period will directly impact the physician's ability to complete other tasks.

We evaluated adverse events defined as endoscopic complications, anesthesia and respiratory complications, and unintended admissions occurring within 72 h of the procedure. We did not evaluate mild adverse events (*i.e.*, nausea, throat pain). There were no procedural, anesthesia and respiratory complications at the community hospital and the ambulatory endoscopy center. Although there were fewer adverse events within the community locations, the number of cases included in this study is too low to determine whether endoscopies in these locations are safer than in a tertiary care facility [16-18]. To make this determination, a large multi-institutional study performed over several years is required. Thus, we only described our experience.

The major strengths of our study were the ability to compare cases performed by each endoscopist between two different locations as well as to compare the ET and PT among all 6 physicians at all three locations. Endoscopic procedures were performed in three clearly delineated locations with the same support staff and the use of strict criteria for scheduling of patients within the community centers. This study due to its retrospective nature has few weaknesses. All cases performed in the tertiary operating



room were not used in the analysis to allow us to match the relatively smaller number of cases at the community sites. However, given that the cases were all conducted within a similar time period and the physicians were all experienced endoscopists, the excluded cases are unlikely to reflect a bias in the results. There was a difference in the allotted time for EGD between the tertiary care operating room and community locations, however we do not believe this had an impact on the study as the procedures were scheduled one after the other with the guidance to perform the subsequent procedure once the operating room was available. Also, the study is underpowered to detect true differences in the rates of adverse events.

CONCLUSION

In conclusion, we found that in select pediatric patient populations, endoscopic procedures can be performed more efficiently in non-tertiary care centers. These data may help future guidelines on building efficient outpatient pediatric endoscopy suites. Further investigation is needed to understand why these procedures are more efficient at community locations. Also, our data forms a foundation upon which further studies can be performed to evaluate whether there is an increased risk to the patient with this practice. Being able to provide more efficient care in a convenient location for selected patients can increase satisfaction while accommodating the increase need for such procedures.

ARTICLE HIGHLIGHTS

Research background

There has been an increase in pediatric endoscopic procedures over time and an increased demand to perform them efficiently. These procedures are now being performed in more diverse clinical settings, from tertiary care operating rooms to ambulatory centers. Data is lacking with regards to safety and efficiency of these procedures across multiple clinical settings which is needed information as the pediatric endoscopic landscape diversifies.

Research motivation

We aimed to understand efficiency and adverse rate events of pediatric endoscopic procedures across multiple clinical settings as there is a paucity of this data in the literature. This research could help lay the foundation for guidelines of building outpatient pediatric endoscopy suites or ambulatory centers.

Research objectives

The main objective of our study was to evaluate the efficiency of endoscopic procedures performed by pediatric gastroenterologists in diverse clinical settings, particularly ambulatory centers as compared to a tertiary care operating room. We also assessed adverse events associated with endoscopic procedures performed across these clinical settings.

Research methods

A retrospective chart review was conducted of esophagogastroduodenoscopy (EGD) or combined EGD and colonoscopies performed over a 4 year period by 6 experienced gastroenterologists in three settings; a tertiary care hospital operating room, community hospital operating room, and a free-standing pediatric ambulatory endoscopy center at a community hospital. Demographics, times, admission rates and adverse events were collected and efficiency was measured in endoscopist time (elapsed time from the endoscopist entering the operating room or endoscopy suite to the next patient entering) and patient time (elapsed time from patient registration to that patient exiting the operating room or endoscopy suite). Statistical analyses were performed by a trained statistician and descriptive statistics were generated for each of the variables collected.

Research results

The majority of the cases were performed at the tertiary care operating room. Endoscopist time at the tertiary care operating room was 12 min longer compared to the community operating room (63.3 ± 21.5 min vs 51.4 \pm 18.9 min; P < 0.001) and 7 min longer compared to the endoscopy center (vs 56.6 \pm 19.3 min; P < 0.001). Patient time at the tertiary care operating room was 11 min longer compared to the community operating room (133.2 \pm 39.9 min vs 122.3 \pm 39.5 min; P < 0.001) and 9 min longer compared to the endoscopy center (vs 124.9 \pm 37.9 min, P < 0.001). Adverse events occurred in 0.1% of cases performed in the tertiary care operating room.

Research conclusions

We found that it was more efficient to perform EGD and colonoscopies at a community hospital



operating room and a free-standing pediatric ambulatory endoscopy center at a community hospital when compared to a tertiary care operating room in a select pediatric population. There was not an increased adverse event rate that we observed at these satellite locations when compared to the tertiary care operating room. Being able to perform these procedures safely and efficiently in multiple clinical settings may help meet the growing demand of endoscopic procedures in children.

Research perspectives

This research showed that pediatric endoscopic procedures are efficient in multiple clinical settings in a select pediatric population. Larger, prospective studies are needed to validate what we have found and to better assess safety. Our research could help lay the foundation for future guidelines on building efficient outpatient pediatric endoscopy suites.

FOOTNOTES

Author contributions: Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS contributed equally to this work; Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS designed the research study; Crawford E and Khalili AS performed the research; Crawford E and Apperson-Hansen C analyzed the data; Crawford E, Sabe R, Sferra TJ, Apperson-Hansen C, and Khalili AS wrote the manuscript; all authors have read and approved the final manuscript.

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Data sharing statement: Data sharing is not permitted for this study.

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