ORIGINAL ARTICLE

Predictive value of colonic transit time indices for differentiating nonnormal from normal sensation in children with chronic functional constipation identified by anorectal manometry

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Background: Constipation is a common disorder in pediatrics, although the underlying pathogenesis is not fully understood. The current study aimed at evaluating the efficacy of different colonic transit time (CTT) indices for differentiating normal from nonnormal sensation in children with chronic functional constipation identified by anorectal manometry (ARM). **Materials and Methods:** In this cross-sectional study, 47 children with chronic idiopathic constipation, aged 5–15 years, were studied. The total and segmental CTTs were estimated by administering multiple radiopaque markers for 6 days and performing a single abdominal radiograph on day 7. Anorectal function was evaluated using manometry with an Arhan probe. The predictive value of CTT indices was evaluated by receiver operating characteristic curve analysis. Area under the curve (AUC) along with 95% confidence interval (CI) as well as sensitivity and specificity was calculated. **Results:** The mean age of the participants was 8.30 ± 2.99 years, with a mean constipation duration of 2.90 ± 0.46; 28 children were identified with nonnormal sensation. The mean values of CTT indices were statistically significantly longer in the nonnormal sensation patients than that in the normal group ($P < 0.001$). In addition, the mean values of manometry parameters were statistically significantly higher in nonnormal sensation patients than that in normal group ($P < 0.01$). Among CTT indices, rectosigmoid CTT (AUC [95% CI] =0.999 [0.99–1]; $P < 0.001$) with sensitivity = 100% and specificity = 94.7% and total CTT (AUC [95% CI] =0.972 [0.93–1] $P < 0.001$) with sensitivity = 82.3% and specificity = 100% had the highest predictive values for differentiating nonnormal from normal sensation patients. **Conclusion:** CTT is a simple and noninvasive technique for classifying patients with constipation. It can be used for identifying children suffering from chronic constipation with nonnormal sensation reliably, instead of ARM. Colonic inertia may be a manifestation of global motility dysfunction. Children with delayed distal colonic transits are more likely to have abnormal defecation dynamics.

Key words: Children, colonic transit, constipation, manometry, predictive value

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INTRODUCTION

Constipation is one of the most common complaints in children, with varying reports of prevalence ranging from 0.7% to 29.6%.[1-3] Between 10% and 25% of all patients who had visited pediatric gastroenterology clinics are those with constipation complaints.[4,5] Nearly 95% of children with this disorder have chronic idiopathic constipation, with unrecognized organic or anatomical cause; although the most widely accepted hypothesis is that fear of defecation and voluntary retention of stools lead to the formation of a functional

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megarectum with loss of rectal sensitivity and of the normal need to defecate, causing overflow incontinence and nonvoluntary expulsion of feces, or encopresis.[6,7]

More than 60% of children with constipation have reported painful defecation before the age of 3 years.[8] However, up to 25% of children have the disorder before 1 year of age, suggesting that voluntary suppression of defecation is not a constant predisposing phenomenon.[1] Improvement is seen in the majority of patients who adhere to treatment recommended by consensus guidelines, including osmotic laxatives and intake of a fiber-rich diet; however, about one-third of children in clinical practice do not respond to conventional treatment, suggesting the existence of other physiopathologic causes.[9] The majority of children suffer functional constipation and do not usually require any diagnostic testing. In patients who do not respond to treatment, the diagnosis is essentially based on clinical history and physical evaluations. Patients and/or their parents refer to the number of stools per week, stool volume, difficulty in defecation, and/or sensation of abdominal fullness.[6] The common symptoms of constipation in children may include passing stool less than three times per week, fecal incontinence, hard stools, excessive straining, or feeling of incomplete evacuation of stool.[10]

The Pediatric Gastroenterology Society, the Rome IV diagnostic criteria, and the Paris Consensus on Childhood Constipation Terminology guidelines support a clinical approach including screening laboratory tests and dietary history along with a detailed physical examination as part of the diagnostic evaluation for constipation.[11-13] As the clinical diagnosis of constipation in children may be difficult because of their inability to describe and report the symptoms, accordingly for children with lack of response to conventional medical treatment or in the presence of a more reliable clinical image, digital rectal examination (DRE) is usually recommended to evaluate either the underlying pathophysiologic mechanisms or a possible organic etiology.

Considering that colonic transit dysfunction is present in 60% of children with refractory constipation and that specific therapies have been proposed for dysfunctional colonic patterns,[11] it would be useful to distinguish them based on a clinical method. Identifying effective diagnostic modalities for children referring to the pediatric clinics with constipation is important. Although during the last decade a remarkable increase in our knowledge of normal and abnormal colonic and anorectal motility in children has been occurred, and a number of different techniques to measure transit and motility have been developed, there is uniformity in the diagnosis of constipation in the outpatient settings. In this regard, several tests including colonoscopy, barium enema, and evaluation of colonic transit time (CTT) by markers and anorectal manometer have been developed to evaluate these complaints.[14]

CTT measurement provides useful information, especially in children with severe and persisting symptoms. The most widely used method to determine CTT in clinical practice is the radiopaque marker (ROM) test. It is inexpensive, is readily available, and provides an accurate approximation of total and segmental CTT. Several ROM test protocols have been suggested, ranging from a single or multiple capsule ingestions followed by single or multiple abdominal X-rays at prespecified times, for example, at 4th day or 4th and 7th days.[15] Overall, CTT is calculated by counting the total number of markers on the plain X-ray, whereas segmental CTT is based on the number of retained markers in three colonic segments, namely right colon, left colon, and rectosigmoid region.[16]

Anorectal manometry (ARM) is a commonly performed test in infants and children with defecation disorders, providing an assessment of sensorimotor activity of the rectum and anal regions. The ARM allows direct measurement of anal resting pressures, anal relaxation upon balloon distension (recto-anal inhibitory reflex [RAIR]), and squeeze pressures, which predominantly reflect internal and external anal sphincter functions. It also indirectly assesses defecation dynamics by measuring the recto-anal pressure gradient during straining and by the rectal balloon expulsion test. The ARM has been found to be a safe test with rare side effects.[17]

Heterogeneity in the population and equipment and methodology used in the various studies do not allow for reliable data for children. Moreover, it is always important to correlate the findings with symptom and severity presentation.[18] To the best of our knowledge, there are no studies from not only in Iran but also in all around the world that compared CTTs in constipated children with nonnormal and normal sensation ones.

The current study's main objectives were to assess whether total and segmental CTT are effective predictors for differentiating constipated children with nonnormal sensation from those with normal sensation identified by ARM and which one has the highest predictive role?

MATERIALS AND METHODS

Study design and participants

In this cross-sectional study, 47 patients with chronic constipation based on the ROM IV, aged 5–15 years, were selected during a 2-year period (2017–2018) from the gastroenterology outpatient units of the Imam Hossein

Pediatric and Children Referral Hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran. We included those patients who had a history of chronic idiopathic constipation for more than 6 months, with or without secondary encopresis, that was refractory to conventional treatment of de-impactation, those who received reeducation of defecatory habits, those who have implemented measures to increase dietary fiber content, and those who had administered mineral oil or osmotic-type laxatives, and those who were not receiving medication except osmotic-type laxatives with effects on the digestive tract at the time of the study. Encopresis was defined as nonvoluntary defecation with a frequency of more than twice weekly in children older than 4 years, in the absence of any underlying organic cause. Children with Hirschsprung disease; those with anal and spinal malformations, metabolic disorders, and a history of colon surgery; those using drugs other than laxatives, and those with mental retardation were excluded from the study.

Ethical approval and consent to participate

The present study obtained the ethical approval from the Bioethics Committee of Isfahan University of Medical Sciences, and all parents gave written informed consent for their children's participation in the current study (study project number: 397193 and research ethic code: IR.MUI.MED.REC.1397.341).

Procedure and evaluations of variables

Anorectal manometry

ARM was performed for all patients using the following protocol by a doctor without any sedation. All children underwent manometry using a water-perfused system (MEDIWATCH UK Limited). ARM was conducted after preparation of the colon with phosphate enema and empty of rectal ampulla was ensured by DRE. A catheter with four radial and four axial channels 1 cm apart was used for perfusion. Pressures were measured by transducers in the perfusion line, perfused with distilled water at a rate of 0.56 mL/min/channel and connected to an MPX 816 processor and Proctomaster 5.0 Dynamed software. Rectal distension was produced with a distending balloon tied to the tip of the catheter. When inserted into the anus, the catheter was drawn and pressure was recorded every centimeter, thus determining the length of the anal canal and the highest pressure zone that characterizes the anal canal. The anal sphincter resting pressure was measured by pulling the catheter out at a rate of 0.5 cm/30 s. The maximal squeeze pressure of the anal sphincter was determined by asking the child to squeeze the sphincter muscles as tight as possible for five times, considering the highest measurement. RAIR was tested by inflating the rectal balloon with 10–50 mL of air. After each 10-mL inflation of the balloon by steps of 30 mL up to a maximum volume of 250, the sphincter pressure was allowed to stabilize to resting pressure values.[19] At each increment of air volume injected in the rectal balloon, the children were asked to report the following sensations: the first feeling of rectal content (first sensation), the first sensation of urgency for defecation (first urge), a steady need to defecate (intense urge), and the painful lasting urge to defecate (maximum tolerable volume). Critical volume (maximum tolerable volume) was defined as the minimum amount of air that produces a lasting urge to defecate. Based on rectal sensation manometric maneuver, we considered a patient as nonnormal sensation when she/he experienced the maximum tolerable volume without reporting any discomfort or desire to defecate which further distention has been aborted.

Colonic transit time

In our study, the CTT was calculated based on the multiple ROM technique described by Arhan *et al*. because this approach needs a single X-ray exposure and reduces the need for repeated referral to the radiology department.[20] Treatment with oral or rectal laxatives was discontinued 5 days before the test. The patients were given six capsules containing ten 1–3-mm-long markers made of an angiographic catheter. The patients took a capsule at 9 am for 6 consecutive days and underwent anteroposterior abdominal control radiographic study on day 7 (at 9:00 AM), using the high-kilovoltage and brief exposure technique (estimated exposure surface, 0.08 mrad/film, i.e., equivalent to one-quarter the exposure of a normal radiograph). All the plain abdominal X-rays were evaluated by a single radiologist. Total and segmental (for the right colon, the left colon, and the rectosigmoid colon) CTTs were calculated by counting the number of markers in each segment and putting it into the following formula: colon transit time = sum of the markers × 2.4.

Statistical analysis

Continuous and categorical data were presented as mean ± standard deviation (or median [range: minimum–maximum]) and frequency percentage. Normality of the continuous data was evaluated by using Kolmogorov–Smirnov test and Q-Q plot, and nonnormally positive skewed data were subjected to logarithmic transformation. Independent samples *t*-test or nonparametric Mann–Whitney U-test was used for comparing continuous normal and nonnormal quantitative data, and Chi-square test or Fisher's exact test was used for comparing categorical data between the nonnormal sensation and normosensitive groups.

The prognostic value of total and segmental CTTs for predicting nonnormal sensation and normosensitive status of patients was evaluated by using receiver operating

characteristic (ROC) curve analysis, and best cutoff values with the highest predictive role for differentiating these two groups of patients based on calculating sensitivity, specificity, and positive and negative likelihood ratios (LRs) were determined. Those values of the CTT indices that maximized the Youden index (sensitivity + specificity – 1) were defined as the optimal cutoff values. The maximum value of the Youden index may be used as a criterion for selecting the optimal cutoff.[21] The Youden index is also defined as "informedness" or the probability of an informed decision (as opposed to a random guess). The area under the curve (AUC) for each CTT parameter was calculated and was compared by using DeLong method. LR for positive test results (LR+) indicates how much more likely the positive test result is to occur in patients with the disease compared to those without the disease; accordingly, LR+ is usually higher than 1, and the higher the LR+, the test is more indicative of a disease. LR for negative test result (LR−) represents the ratio of the probability that a negative result will occur in patients with the disease to the probability that the same result will occur in people without the disease; LR − is usually <1, and the lower the LR−, the lower the posterior LR of the studied person having the disease.[21] All statistical analyses were performed by using STATA software (StataCorp LP, 2015, Stata Statistical Software: Release 14. College Station, TX, USA).

RESULTS

In the current study, 47 children fulfilled the study's inclusion criteria and were recruited. The mean patient age was 8.30 ± 2.99 years (median = 7; range: 5–15 years), out of which 25 (53.2%) were female and 38 (80.1%) were with a breastfeeding history. The mean values of weight, constipation duration, age of defection control, and urine control were 27.09, 2.90, 2.12, and 2.65 years, respectively. The two groups, i.e., normal and nonnormal sensation, were comparable in terms of demographic and past history of basic characteristics ($P > 0.05$).

Table 1 and Figure 1 show CTT indices for both groups. The mean total CTT and the segmental left and right colon and rectosigmoid CTTs were statistically significantly longer in the patient group with nonnormal sensation than that in the normal sensation group ($P < 0.001$). In addition, the mean values of manometry parameters were statistically significantly higher in nonnormal sensation patients than that in normal sensation group ($P < 0.01$).

The ROC curves for a comparative assessment of predictive role of CTT indices were calculated and compared [Figure 2 and Table 2]. AUCs clearly indicated that AUCs for four indices were significantly different, indicating different ability of these indices for differentiating children with normal sensation from nonnormal sensation children; although all indices have statistically significant AUCs ($P < 0.01$). The best CTT index was rectosigmoid colon with an AUC = 99.9% followed by total CTT with an AUC = 97.7; there was no statistically significant difference between AUCs of rectosigmoid colon and total CTT ($P > 0.1$). The AUCs for left and right CTTs were 84.3 and 93.9, respectively, that they were not statistically significantly different ($P > 0.1$). However, the AUCs for rectosigmoid colon and total CTT were statistically significantly higher than AUCs for left and right CTTs ($P = 0.01$). Assessment of the best CTT cutoff values by the Youden index confirmed 12, 7, 21, and 54.2 h for left, right, rectosigmoid, and total CTTs, respectively. The specificity and sensitivity of the proposed CTT variables in the identification of the children of the two groups are shown in Table 2. Sensitivity, i.e., the percent association with a correctly identified nonnormal sensation, for rectosigmoid colon, was the highest among all CTT variables; 100%, with a value >21 h, clearly indicating an optimal association of this variable with a well-differentiated nonnormal sensation patients from normal sensation group; after that, the total CTT had the highest sensitivity, i.e., 89.29; cutoff value: 54.2 h, and both indices had the highest specificity, i.e., the percent association with a correctly identified nonnormal sensation was 94.74% and 100%, respectively. The left CTT and right CTT also had acceptable predictive role, in which the left CTT with a cutoff value of 12 h had a sensitivity of 82.14 and a specificity of 73.68, whereas the right CTT had a sensitivity of 71.43 and a specificity of 78.95 with a cutoff value of 7 h. All the four CTT variables had acceptable values for both LR + and LR−, indicating high levels of correct classification ability [Table 2].

DISCUSSION

Constipation is a frequent gastrointestinal disorder among children, which is estimated to occur in 5%–10% of

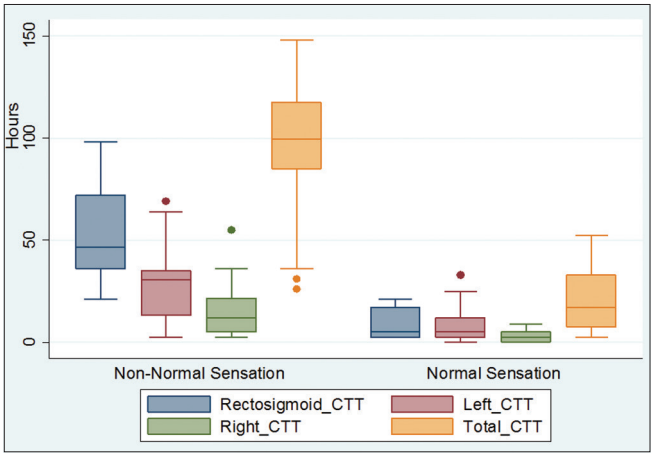

Figure 1: Box plot of different colonic transit time indices for the two study groups

Table 1: Basic demographic and clinical characteristics of total sample and normosensitive and nonnormal sensation patients

Variables	Total sample	ARM results		*P**
		Nonnormal sensation (*n*=28)	Normosensitive (*n*=19)	
Gender				
Male	25 (53.2)	14 (50)	11 (57.9)	0.59
Female	22 (46.8)	14 (50)	8 (42.1)	
Breastfeeding (yes)	38 (80.9)	22 (78.6)	16 (84.2)	0.63
Age (year)	8.30±2.99 7 (5-15)	8.39±3.34 7 (5-15)	8.16±2.46 7 (5-14)	0.79
Weight (kg)	27.09±10.03 23 (15-55)	27.5±9.71 23.50 (15-45)	26.47±10.73 23 (17-55)	0.74
Constipation duration (year)	2.90±0.46 3 (1-8)	3.07±1.65 3 (1-8)	2.74±0.93 2 (2-5)	0.43
Age of urine control (year)	2.12±0.46 2 (1-4)	2.13±0.54 2 (1-4)	2.12±0.16 2 (2-4)	0.96
Age of defection control (year)	2.65±0.98 2 (2-5)	2.87±1.12 2 (2-5)	2.31±0.16 2 (2-4)	0.07
CTT parameters (h)				
Left CTT	19.06±17.15 14.50 (0-69)	26.61±17.30 30.50 (2-69)	7.95±9.15 5 (0-33)	<0.001
Right CTT	10.65±11.85 7 (0-55)	15.57±13.10 12 (2.5-55)	3.39±2.81 2.5 (0-9)	<0.001
Rectosigmoid CTT	35.72±27.87 29 (2.5-98)	53.43±22.02 46.5 (21-98)	9.63±7.13 5 (2.5-21)	<0.001
Total CCT	65.44±45.28 57 (2.5-148)	95.61±31.69 99.50 (26-148)	20.97±15.20 17 (2.5-52)	<0.001
Sensation parameter (mL)				
First	81.28±63.71 50 (50-250)	102.50±75.89 55 (50-250)	50±0 50 (50-50)	0.004
Urge	168.93±65.81 150 (90-250)	215.50±48.35 250 (100-250)	104.75±16.11 100 (90-150)	<0.001
Maximum	212.77±47.17 250 (150-250)	250±0 250 (250-250)	157.89±18.83 150 (150-200)	<0.001

**P* values resulted from two independent samples *t*-test or Mann–Whitney U-test and Chi-square test for continuous and categorical variables, respectively. Values are mean±SD or media (minimum–maximum) and frequency (%) for continuous and categorical variables, respectively. CCT=Colonic transit time; SD=Standard deviation, ARM=Anorectal manometry

Table 2: Area under the curve and predictive indices of different colonic transit time indices for differentiation of nonnormal sensation children from normal sensation constipated children

Variables	AUC (95% CI)	Cutoff value	Sensitivity	Specificity	LR+	LR−	*P*	*P*
Left CTT	0.843 (0.72-0.96)	12	82.14	73.68	3.12	0.12	<0.001	0.01
Right CTT	0.839 (0.73-0.95)	7	71.43	78.95	3.39	0.36	<0.001	
Rectosigmoid CTT	0.999 (0.99-1)	21	100	94.74	19.00	0.00	<0.001	Total CTT and rectosigmoid colon indices are different from left and right CTTs
Total CCT	0.972 (0.93-1)	54.2	89.29	100	16.96	0.11	<0.001	

CCT=Colonic transit time; AUC=Area under the curve; CI=Confidence interval; LR=Likelihood ratio

children all over the world. Most children with functional constipation do not usually require any diagnostic evaluation. For those patients who do not respond to conventional medical treatments or in the presence of a gold standard approach for diagnosis, accurate, noninvasive, low-cost, instrumental assessments are usually recommended for elaborating either the underlying pathophysiologic mechanisms or a possible organic etiology. Among the different diagnostic approaches, CTT measurement provides useful information, especially in children with severe and persisting symptoms. It is inexpensive, is readily available, and provides an accurate approximation of total and segmental CTTs.[14]

Overall, CTT is calculated by counting the total number of markers on the plain X-ray, whereas segmental CTT is based on the number of retained markers in three colonic segments, namely right colon, left colon, and rectosigmoid region.[16] In addition, ARM is a noninvasive procedure that frequently performs motility study in children and helps to explain the mechanisms of defecation disorders because of hypertonia, low tone, or paradoxical shrinkage through

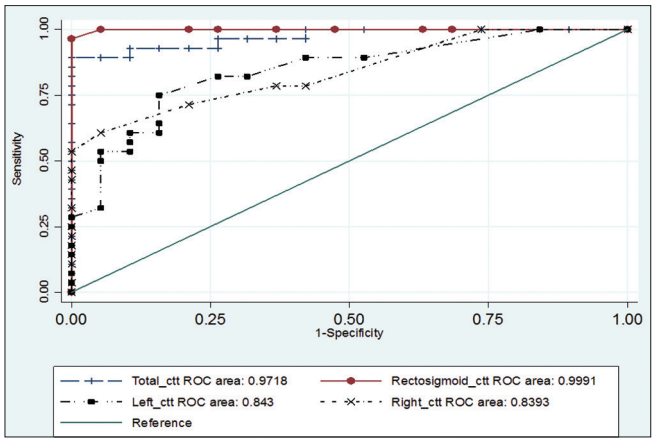

Figure 2: Receiver operating characteristic curves of all colonic transit time indices for discriminating nonnormal sensation from normal sensation constipated children

assessing anorectal sensations, pressure changes, and rectal compliance.[22] ARM helps in the assessment of sphincter function as well as anorectal sensation in children with chronic constipation and fecal incontinence. In the current study, we divided 47 children with chronic idiopathic constipation into normal sensation ($n = 19$) and nonnormal sensation ($n = 28$) children by using ARM and evaluated the predictive role of different CTT indices for differentiating between these two groups. All indices including total, left, right, and rectosigmoid CTT showed high prognostic value with high predictive indices. Our study also showed that all CTT indices were significantly more prolonged in nonnormal patients than normal sensation ones.

Previous studies on children and adults used CTT approach;[7,23-25] however, majority of them were analyzed in a case–control design setting, in which they compared the CTT indices between constipated children and healthy children. In contrast, we used this approach on chronically constipated children divided by ARM into normal sensation and nonnormal sensation groups. As proposed by Bouchoucha *et al.*, this modality enables clinicians to eliminate the need for subsequent radiography evaluation in individuals with slow transit times, when the markers are ingested for 6 days and a simple abdomen plate was performed at day 7.[26] This approach allows estimating the value of total CTT of up to 144 h if all the markers are retained on day 7; among our included patients with constipation, only two patients were observed with value close to 144 h, and majority under 100 h, thereby eliminating the need for a second abdominal radiography after 10 days.

Our results showed that an abdominal X-ray examination with the use of radiopaque markers at intake had significant predictive value even more than those studies that evaluated the CTT indices for differentiating constipated children from healthy controls.[7,27,28] Measurements of CTT predicted nonnormal sensation constipated children from normal sensation children if their values were more than 12, 7, 21, and 54.2 h for left, right, rectosigmoid colon, and total CTT, respectively. In addition, our results showed that the mean values of CTT indices are longer in nonnormal patients than normal sensation ones. This means that CTT indices allow the differentiation between children with normal sensation and nonnormal sensation constipation; similar findings have been reported in some previous studies, although they compared healthy controls with constipated children.[6,29-33] Our findings, reinforced the previous studies that concluded in children with functional constipation is a good correlation between CTT indices and clinical symptoms.[14,34] Accordingly, it has been suggested that children with different subgroups of constipation such as nonnormal/normosensitive, pancolonic transit delay, and rectosigmoid transit delay might benefit from different treatment approaches.[14,35] Furthermore, the different prognostic values of CTT indices in our study and previous studies provide the rationale for assessing total and segmental CTTs in constipated children.[36]

A direct comparison of CTT values, particularly normal ones from other studies with those of our study, is not possible because our study participants were all chronic constipated patients, although important data about both total CTT and segmental transit time are similar to those of previous studies in constipated children. Segmental transit time was found to be longest in the rectosigmoid region, which corresponds with that of previous studies.

To the best of our knowledge, there are no studies from not only in Iran but also in all around the world that compared CTTs in constipated children with nonnormal and normal sensation ones. Hence, our study provides an important finding that chronically severe constipated patients with nonnormal sensation have longer total and all segmental transit time in comparison with those of normal sensation patients.

The limitation of our study is lack of a healthy control group for comparison and estimation of the prevalence of patients outside of the normal range of transit time. The CTT is affected by age as well as gender; accordingly, we estimated the predictive values of CTTs with adjusting these variables as confounders. Radiopaque marker for CTT is a simple and reliable technique for the evaluation of normal and nonnormal sensation in children with chronic constipation.

Future research will be needed to answer the ambiguity about the evolution of CTT over the times as well as the impact of treatment on CTT.

CONCLUSIONS

CTT is a simple and noninvasive technique for classifying patients with constipation. It can be used for identifying children suffering from chronic constipation with nonnormal sensation reliably, instead of ARM. Colonic inertia may be a manifestation of global motility dysfunction. Children with delayed distal colonic transits are more likely to have abnormal defecation dynamics. Larger population-based studies are needed to be performed in countries such as Iran. For evaluating defecation patterns in different populations including healthy children and children with functional constipation and in different sex and age groups. So in combination with a careful analysis of the diet, and using the same methods to evaluate colonic transit to provide more reliable data on the efficacy of CTT as a easily applicable approach in day-to-day clinical practice, to more clearly define patients with this disorder and to improve therapy and follow-up. A global delay in CTT may suggest the presence of a more generalized alteration in colonic motility, amenable to treatment with prokinetic drugs. However, recording delayed distal transit patterns suggests the need to investigate possible anorectal functional anomalies, with the use of biofeedback techniques that involve CTT and ARM to help these children in order to recover their normal defecatory mechanisms.

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Conflicts of interest
There are no conflicts of interest.

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