Feasibility of Simple Oral Preparation Contrast-Enhanced CT Colonography (SOP-CE-CTC) Using Mannitol as a Neutral Oral Contrast Agent

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Abstract

Keywords
► simple oral preparation contrast-enhanced CT colonography (SOP-CE-CTC)
► mannitol
► colonic distension
► bowel preparation
► mural visualization
► colorectal cancer screening

Purpose   This article prospectively assesses the feasibility of simple oral preparation contrast-enhanced computed tomography colonography (SOP-CE-CTC) using a large volume of oral 3% mannitol for good colonic distension along with mural and mucosal fold visualization.

Methods   A total of 100 patients in whom contrast CT abdomen was requested, recruited as per selection criteria, were advised to take mild oral bowel preparation for two nights, prior to the investigation. Then, after fasting overnight, they were asked to consume 1,500 to 2,000 mL of 3% mannitol solution in about an hour. Thirty minutes after completing the ingestion of oral mannitol, intravenous contrast was injected and SOP-CE-CTC was acquired at 55 seconds. Distension of six segments of the colon was evaluated by assigning scores 1 to 4 for qualitative assessment; and measuring the maximum luminal diameter of the colon, for quantitative assessment. Colonic mucosal and mural visualization were evaluated subjectively. All observations were recorded by two reviewers (with varying levels of experience) independently.

Results   On qualitative analysis, the colon showed optimal distension (score 4) in 58 to 89% cases on SOP-CE-CTC. There was agreement between both the reviewers in 89 to 99% cases (weighted kappa 0.820–0.979; $p < 0.001$). On quantitative analysis, the mean of the maximum colonic diameter ranged between 3.4 and 5.2 cm; and both the reviewers agreed in 89 to 97% cases (weighted kappa 0.777–0.967; $p < 0.001$). Mural and mucosal fold visualization in the proximal four segments of the colon was excellent (in 90–98%) but in the rectum and sigmoid it was 45 and 66%, respectively; both the reviewers agreed in 100% cases (weighted kappa 1.0 and $p < 0.001$).

Conclusion   Good colonic distension, mural, and mucosal fold visualization can be achieved on SOP-CE-CTC using 1,500 to 2,000 mL of 3% oral mannitol and mild oral bowel preparation agents.

Introduction

Diseases of the large bowel like colorectal carcinomas,[1] adenomas, and other types of polyps, inflammatory bowel diseases, and tuberculosis (TB), in India, are a common cause of significant morbidity and mortality. Colonoscopy is the gold standard for diagnosis of large bowel diseases, as it incorporates the ability to perform a biopsy or excision. However, it is an invasive procedure which involves extensive catharsis, colon instrumentation, and insufflation, risks of serum electrolyte disturbance, renal failure, perforation, and anesthesia/sedation, especially in those who are frail and elderly.[1]

Computed tomographic colonography (CTC), a structural examination of the colon similar to optical colonoscopy, is an alternative investigation for patients who refuse to undergo the latter and in patients with failure of colonoscopy. CTC is also useful in conditions where colonoscopy is contraindicated or not possible.[2]

Adequate luminal distension is a critical issue for CTC, because incomplete distension of the colon may simulate several pathologic conditions (e.g., inflammatory bowel disease and an annular cancer) or hide the presence of tumors or polypoid lesions.[2] In CTC distension is achieved by automated administration of carbon dioxide (CO_2) or air,[3] which can cause abdominal pain or discomfort in some patients; in addition to the inconvenience and embarrassment of rectal catheterization. Rarely, vasovagal reaction and colon perforation[4] have also been reported with CTC. Bowel preparation also represents an essential component of CTC, as its accuracy is highly dependent on the adequacy of colonic cleansing. Successful bowel preparation mainly depends on the patient's compliance and the majority of patients undergoing CTC find this the most unpleasant part of the examination.[5]

During CT enterography with mannitol for assessment of distension, mucosal fold, and mural visualization of the small bowel, distension of the proximal large bowel was also observed. This was attributed to delayed acquisition time, the altered volume of mannitol used, nonabsorbable nature, and high osmolarity of mannitol.[6] Therefore, the present study was designed based on the hypothesis that use of large volume of mannitol and a delay in CT acquisition may lead to optimum distension of large bowel.

This procedure was named "simple oral preparation contrast-enhanced CTC" (SOP-CE-CTC) and was performed simply using mild oral bowel preparation agents, oral 3% mannitol solution, and an intravenous contrast agent. SOP-CE-CTC aims to completely eliminate the administration of negative contrast agents per rectally. This method has the potential of creating a paradigm shift in large bowel imaging by maximizing patient comfort, without compromising the quality of information derived from the study.

Methods

Patients

Institutional ethics committee approval and written informed consent from the patient or attendant was obtained. Adult patients above 18 years of age referred for CECT of the abdomen and pelvis at our institution, for any indication other than bowel-related diseases, and having no previous history of bowel surgery, were included in the study during the period November 2018 to May 2020. Patients who were to undergo surgery for emergency indications, perioperative patients, pregnant patients, and children who may not tolerate abdominal distension; patients with a large intra-abdominal mass that could hamper large bowel distension; patients allergic to intravenous contrast agents; or patients in whom oral mannitol was contraindicated were excluded from the study. Patients found to have ileocecal TB on CECT were also excluded.

The patients were advised to take two bisacodyl tablets (5.0 mg each) orally, after dinner on two nights, prior to SOP-CE-CTC. They were allowed to eat regular meals on the day before the procedure and reported to the CT scan suite fasting overnight. Here, the patients were offered 1,500 to 2,000 mL of 3.0% mannitol solution to drink over 45 to 60 minutes. SOP-CE-CTC was acquired 30 minutes after completing the consumption of mannitol.

Imaging Protocol

Scans were acquired in the supine position alone, on 64-slice multidetector CT (Somatom Definition AS, Siemens AG, Germany) with a slice thickness of 3.0 mm, reconstructed at 1.0 mm interval, as per the protocol dictated by the indication of CECT, and image acquisition at 55 seconds from the beginning of injection of intravenous contrast medium was mandatory. Note that 100 to 150 mL of intravenous contrast agent was injected at the rate of 2.5 to 3.0 mL/s. The patients were closely monitored up to half an hour after the procedure, for any untoward effects, and telephonically thereafter for 24 hours.

Analysis

Patients with an incidental finding of ileocecal wall thickening due to TB on CECT abdomen, were not evaluated further, as it was believed that the inflammation could prevent adequate colonic distension. Hence, out of 120 patients recruited for the study as per selection criteria, only 100 underwent further analysis.

Axial CECT images and multiplanar reconstructions in coronal and sagittal planes were reviewed by an experienced radiologist (29 years' experience) (Reviewer 1 [R1]) and a postgraduate student of radiology in her third year of residency program (Reviewer 2 [R2]) on the CT workstations, independently. Both R1 and R2 had a shared experience of CTC interpretation in 30 cases, prior to the evaluation of the 100 study cases. Qualitative and quantitative assessment of six different segments of the large bowel, that is, rectum, sigmoid colon, descending colon, transverse colon, ascending colon, and cecum, were done. For qualitative analysis "scores" were assigned based on subjective evaluation of the extent of distension of various segments of the large bowel[7] (►**Fig. 1**).

- Score 1: Complete collapse: Lumen was not seen/just seen; wall may or may not be discernible, fold pattern may not be recognized.
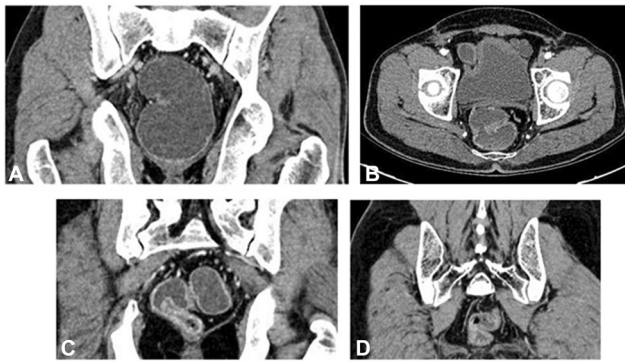
Fig. 1 Qualitative "scores" assigned to extent of distension of the rectum (**A**) score 4, (**B**) score 3, (**C**) score 2, and (**D**) score 1.

- Score 2: Partial collapse: Lumen was visible, but distension was poor/haustra seen attaching at the center line ("kissing folds").
- Score 3: Reasonable but suboptimal distension: Lumen distended, but folds are not well separated; haustra were slightly bulbous.
- Score 4: Optimal distension: Segment was well distended, the wall was uniformly visualized, fold pattern could be clearly recognized; haustra were sharply defined/thin.

The most collapsed portion of any individual segment was used to assign the overall score for distension of a segment of colon.

For quantitative analysis, the maximum luminal diameter perpendicular to the long axis of a particular segment of the colon was measured in centimeters using calipers (►**Fig. 2**).

Good colonic mucosal and mural visualization was mentioned as "yes" or "no" on contrast-enhanced scans.[8] The presence or absence of fecal residue in various segments of the colon was also recorded.
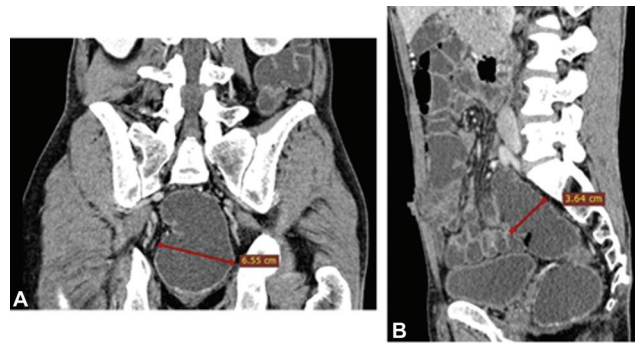
Fig. 2 Maximum luminal diameter measured perpendicular to long axis of (**A**) rectum and (**B**) sigmoid colon in centimeters, using calipers.

Statistical Analysis

Descriptive data was expressed as mean ± standard deviation. For interobserver agreement between R1 and R2, the kappa coefficient was calculated for each of the following parameters: large bowel distension, mucosal fold visualization, and mural visualization. p-Value of < 0.05 was considered as statistically significant.

Results

The age of the patients ranged from 18 to 70 years. The mean age was 36 years. There were 60 males and 40 females.

The indications for CECT abdomen in our study were abdominal TB ($n = 17$), acute pancreatitis ($n = 14$), gallbladder (GB) disease ($n = 13$), space-occupying lesions in liver ($n = 11$), kidney ($n = 4$), and pancreas ($n = 2$), gynecological causes ($n = 9$), metastatic work up ($n = 8$), pyrexia of unknown origin ($n = 8$); follow-up of liver and splenic injury ($n = 6$), retroperitoneal metastasis ($n = 5$), obstructive jaundice ($n = 2$), and lymphoma ($n = 1$).
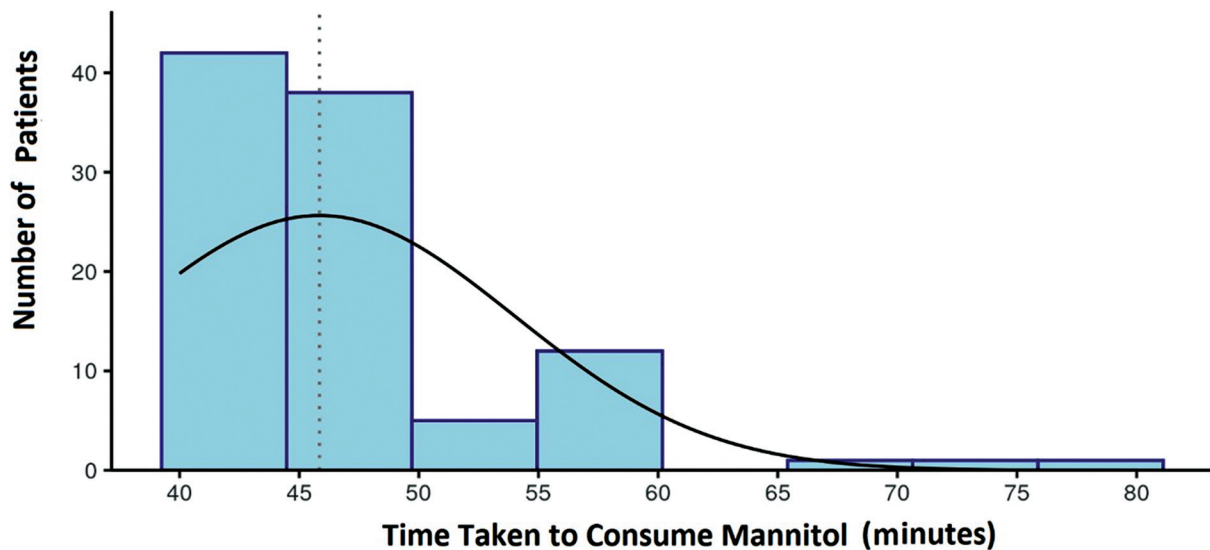
Fig. 3 Histogram representing time taken to consume 1,500–2,000 mL of 3.0% oral mannitol in simple oral preparation contrast-enhanced computed tomography (CECT) colonography.

Fig. 4 Colonic distension with excellent mucosal and mural fold visualization on simple oral preparation contrast-enhanced computed tomography colonography (SOP-CE-CTC) (arrows) in (**A**) cecum, (**B**) ascending and descending colon, (**C**) transverse colon, (**D**) sigmoid colon, and (**E**) rectum.

The time taken to consume 1.5 to 2.0 L mannitol ranged between 40 and 80 minutes. The mean time of mannitol consumption was 45.85 minutes (►**Fig. 3**). In 78% patients it was ≤ 50 minutes.

Qualitative Analysis (Supplementary ►Fig. S1, available in the online version only)

Both the reviewers (R1 and R2) observed that all parts of the colon showed optimal or excellent distension (score 4) on SOP-CE-CTC, in the majority of the patients, that is, cecum (R1 and R2, 73%), ascending colon (R1and R2, 89%), transverse colon (R1, 79%, R2, 77%), descending colon (R1 and R2, 85%), sigmoid colon (R1, 59%, R2, 60%), and rectum (R1, 62%, R2, 58%). Score 3, that is, reasonable but suboptimal distension of the colon, was the next most common observation on SOP-CE-CTC.

Partial collapse was seen in 2 to 10% of cases (maximum in the transverse colon followed by the sigmoid colon). Complete collapse was seen in 4 to 5% cases in rectum; and one case each in cecum, ascending colon, and sigmoid colon.

Quantitative Analysis

On SOP-CE-CTC, maximum distensibility was seen in the ascending colon followed by cecum. Transverse colon and rectum also showed good distension. Sigmoid colon and descending colon showed least distensibility in SOP-CE-CTC. The mean of maximum diameter of various segments of colon measured by R1 and R2 are demonstrated in ►**Supplementary Fig S2**, available in the online version.

Mural and Mucosal Fold Visualization

There was excellent mural and mucosal fold visualization (►**Fig. 4**) in the majority of patients (90–98%) in all the six segments of the colon on SOP-CE-CTC. In 55% patients the mural and mucosal fold visualization was compromised in the rectum, and in 34% patients in the sigmoid colon (►**Table 1**).

Patient Problems in SOP-CE-CTC

Some patients suffering from various abdominal diseases for which CT was requested, complained of a few problems

Table 1 Colonic mucosal fold and mural visualization and reasons for their nonvisualization on simple oral preparation contrast-enhanced computed tomography (CECT) colonography

Serial no.	Segment of colon	Mural and mucosal fold visualization	Mural and mucosal fold nonvisualization	
			Fecal residue present	Collapse of lumen
1.	Rectum	45	50	5
2.	Sigmoid colon	66	33	1
3.	Descending colon	90	10	0
4.	Transverse colon	97	3	0
5.	Ascending colon	97	2	1
6.	Cecum	98	1	1

Table 2 Distribution of problems reported by patients during simple oral preparation CECT colonography ($n = 100$)

Problems encountered during simple oral preparation CECT colonography	No. of patients
Pain abdomen (mild/moderate/severe)	20
Vomiting	11
Nausea	9
Diarrhea	5

Abbreviation: CECT, contrast-enhanced computed tomography.

during the procedure, while drinking the mannitol solution, which are depicted in ►**Table 2**.

Statistical Analysis

There was agreement between both the reviewers in 89 to 99% cases for qualitative assessment of colonic distension, the weighted kappa ranged between 0.820 and 0.979 and p-value was < 0.001. On quantitative analysis there was a very strong correlation between both the reviewers. Weighted kappa was 0.777 to 0.967, interclass coefficient ranged between 0.95 and 0.99, and p-value was < 0.001. There was 100% agreement between both the reviewers ($p \leq 0.001$ and weighted kappa $= 1$) for mural and mucosal fold visualization.

Discussion

Colonic cleansing represents the most unpleasant step of CTC.[3] Bowel cleansing agents for CTC cause symptoms such as intense watery diarrhea, abdominal discomfort, bloating, pain, nausea, and vomiting. Research is therefore aimed at developing less invasive preparations (so-called "reduced-cathartic") or even eliminating the need for bowel preparation at all ("prep-less" approach).[5] Although excellent colon distension can be achieved with automated CO_2 insufflation which is tolerated well by most patients, discomfort of rectal catheterization and side effects like vasovagal reaction and colon perforation have been reported with standard CTC (►**Table 3**).

On SOP-CE-CTC using oral mannitol as a neutral contrast agent in patients with abdominal diseases (excluding bowel disorders), it was possible to obtain optimal or excellent distension of all six colonic segments in 58 to 89% cases on qualitative assessment, and reasonable distension in another 7 to 34% cases. This assessment had been done by two independent reviewers with variable experience: one having a radiology experience of 29 years, while the other had 3 years' experience only. The mean maximum colonic diameter in various segments was also optimal and ranged from 3.4 to 5.2 cm; so with contrast enhancement the mural and mucosal fold visualization was also good. There was negligible difference in the quantitative analysis by both reviewers, and the difference in measurements was not statistically significant (p-value < 0.01). Collapse of the lumen of large bowel contributed to prevention of wall delineation and mucosal fold visualization in only 6% patients.

The high osmotic effect of mannitol is considered important for bowel distension. Oral mannitol produces uniform intraluminal attenuation, high contrast between luminal content and bowel wall, minimal mucosal absorption leading to maximum distension, absence of any artifact formation, and no significant adverse effects.[6] No control group was used for comparison of distension with mannitol, as poor colonic distension was observed in routinely done abdomen CT scans after oral administration of plain water only.

Bowel preparation which is a major determinant for successful evaluation of the colonic mucosa usually depends on the patient's compliance. No agreement has been reached about the ideal bowel preparation technique and there is great variability in preparation strategies.[5] In our study, we simply prescribed two tablets of bisacodyl to be taken for two nights before the scheduled appointment for SOP-CE-CTC. This simple method of bowel preparation was well tolerated, so the compliance of all the patients in our study was excellent.

Minimal preparation CTC (MPCTC) protocol limited to an extended fecal tagging protocol reviewed by Meiklejohn

Table 3 Differences between CTC with rectal insufflation/contrast and simple oral preparation CE-CTC

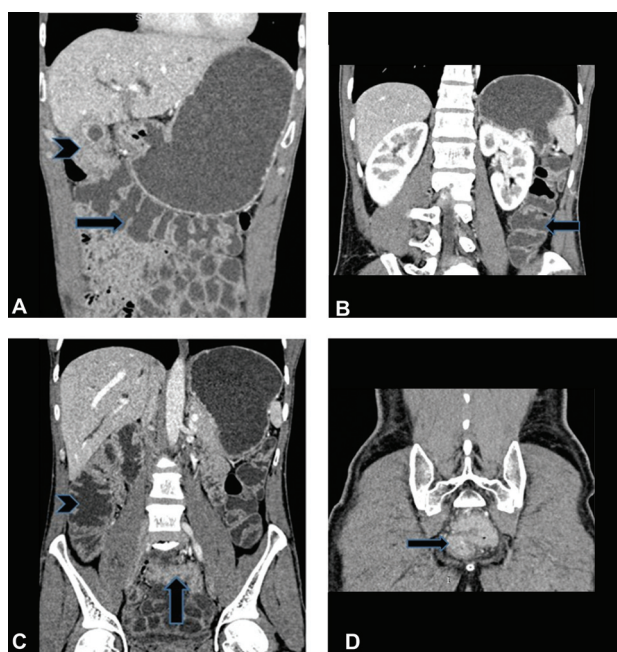| Conventional CTC	Simple oral preparation CECT colonography
1. Invasive technique	1. Noninvasive technique
2. Very low risk of colonic perforation (0.005–0.03%)[9]	2. No risk of colonic perforation
3. Rectal catheter can obscure or efface a pathologic lesion[10]	3. No rectal catheter used
4. Scanning in prone and supine positions increases the radiation dose to the patient[9]	4. Scan done in only supine position (in this preliminary study), so radiation dose is less
5. Can rule out small polyps	5. Can be more useful in detecting larger colonic lesions
6. Oral contrast tagging can allow clear distinction of residual adherent stool in the colon[10]	6. Fecal tagging was not used in this preliminary study
7. Procedure completed in 15–20 min	7. Patient waiting time is long, including time for consumption of mannitol
8. Discomfort involves postprocedure bloated sensation .	8. Patients may have diarrhea or vomiting

Abbreviations: CECT, contrast-enhanced computed tomography; CTC, computed tomographic colonography.

Fig. 5 Fecal matter in (**A**) rectum (arrow) and (**B**) sigmoid colon (arrow) make wall assessment difficult, although the distension of rectum and sigmoid is adequate.

et al[1] used neither catharsis nor insufflation, and achieved a high negative predictive value of 0.99 (95% confidence interval 0.97–1.01) in detecting colorectal cancer (CRC) in symptomatic elderly and frail patients. However, MPCTC had a low sensitivity for smaller lesions, as unlike our study no intravenous contrast was used in MPCTC nor was an attempt made to distend the large bowel.

The use of intravenous contrast in SOP-CE-CTC led to excellent mucosal and mural fold visualization, which combined with optimal distension of the large bowel using mannitol, can achieve better detection of polyps or small lesions. In our study, the mural and mucosal fold visualization was excellent (90–98%) in the proximal four segments of

the colon, while visualization in the rectum and in the sigmoid colon was 45 and 66%, respectively, predominantly due to the presence of fecal residue (►**Fig. 5**).

Among the 20 patients who complained of abdomen pain of varying severity, with or without associated nausea, vomiting, and diarrhea, while consuming mannitol solution during SOP-CE-CTC, in 16 patients there was adequate distension (score 3 and score 4) of most of the colonic segments. Probably depletion in the volume of mannitol due to vomiting or diarrhea was small and allowed optimal distension of most segments of the colon in these patients. Presumably, diarrhea resulted in a decrease in the residual volume of mannitol and thereby reduction in its osmotic effect in 6 patients, causing collapse of the rectum and sigmoid colon, while the rest of the colonic segments showed adequate distension (score 3 and 4) (►**Fig. 6**).

Hepatomegaly cannot be considered as the reason for complete collapse of the right side of colon due to compression (►**Fig. 7**), as six patients in our study had hepatomegaly (craniocaudal length = 19.0–22.0 cm) due to various causes such as liver metastasis, multiple liver abscesses, hepatocellular carcinoma in cirrhotic liver, etc.; but in four of them, in

Fig. 6 (**A**) Wall thickening of hepatic flexure (arrow-head) was seen due to infiltration by carcinoma gallbladder, however, the distension of transverse colon (arrow), (**B**) descending colon (arrow) and (**C**) ascending colon (arrow head), was not compromised. (**C**) Complete collapse of the sigmoid colon (arrow) and (**D**) rectum (arrow) seen as patient had two bouts of diarrhea after consuming 2 L of mannitol, before simple oral preparation contrast-enhanced computed tomography colonography acquisition.

Fig. 7 A 60-year male, a known case of carcinoma lung showing gross hepatomegaly with liver metastasis and gross ascites. Patient complained of moderate abdomen pain and had two episodes of vomiting during simple oral preparation contrast-enhanced computed tomography colonography (SOP-CE-CTC). (**A**) Both cecum and ascending colon showed complete collapse (arrow), (**B**) descending colon and sigmoid colon showed partial collapse (arrow) (score 2). (**C**) However, transverse colon (arrow) showed reasonable but suboptimal distension (score 3) and (**D**) rectum (arrow) showed optimal distension (score 4).
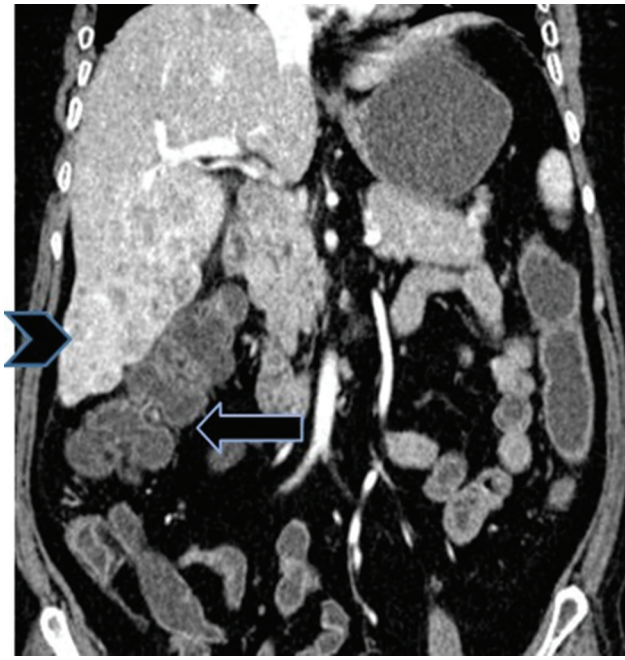
Fig. 8 Score 3—Suboptimal but reasonable distension of ascending colon (arrow) seen in hepatomegaly with liver metastasis (arrow head).

Fig. 9 In a case of hepatomegaly with (**A**) multiple liver abscesses (arrow), (**B**) cecum (arrow head) and ascending colon (arrow) show inadequate distension (score 2), may be due to inflammatory changes in the adjacent colonic wall. Rest of the colonic segments (**C**) transverse colon (arrow), (**D**) sigmoid colon (arrow), and rectum (arrow head) showed excellent distension (score 4).

spite of hepatomegaly, there was reasonable distension (score 3) of the adjacent ascending colon (►**Fig. 8**).

In the sixth patient with hepatomegaly due to multiple liver abscesses, ascending colon and cecum were assigned score 2. This inadequate distension may be due to inflammatory changes in the colonic wall adjacent to the liver abscess, because the transverse colon and rectum distant from the liver showed excellent distension (►**Fig. 9**). Similarly, collapsed rectum and sigmoid colon (score 1) was also seen in a young patient with bilateral tubo-ovarian abscesses, probably due to pelvic inflammatory disease, as the wall of the rectum and sigmoid colon showed mural thickening with stratification, while the remaining segments of the colon showed optimal distension with mannitol (►**Fig. 10**). Thus, as infective/inflammatory disorders are unlikely to be confounding factors in patients undergoing screening for CRC, the technique of SOP-CE-CTC may be more successful in them.

Interestingly, the presence of a partial stricture in the bowel, did not prevent the distension of the distal large bowel in SOP-CE-CTC. Despite GB malignancy infiltrating and causing a narrowing of the lumen of the adjacent hepatic flexure, optimal distension of the proximal colon (►**Fig. 7**) and colon distal to the malignant stricture (excluding rectosigmoid) was possible on SOP-CE-CTC. A similar observation was made in some patients with ileocecal TB. Twenty patients with suspected abdominal TB in whom thickening of terminal ileum and cecum was seen on CECT, were not evaluated further in our study, as it was presumed that the luminal narrowing may not allow the mannitol to pass freely into the large bowel and would thus compromise the colonic distension on –SOP-CE-CTC. However, we observed adequate
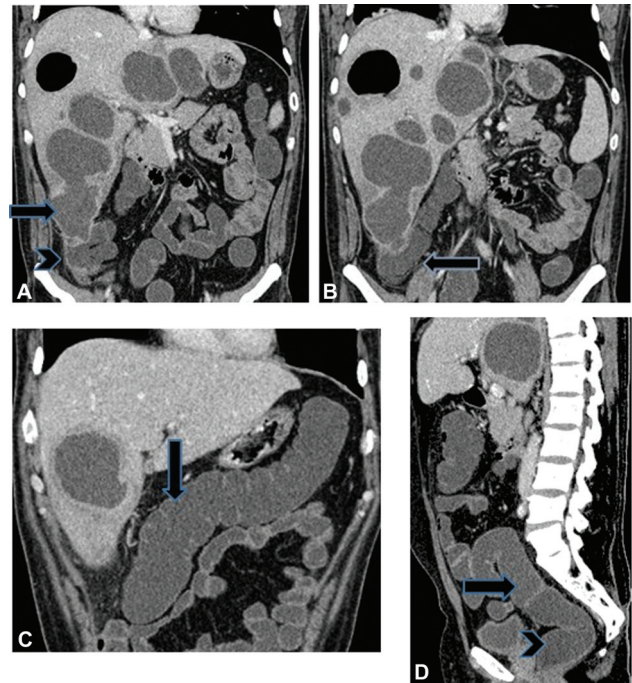
distal colonic distension in cases of ileocecal TB, as had been reported by Prakashini et al.[6]

A major limitation of our study was that SOP-CE-CTC was performed in patients with existing comorbidities (e.g., pancreatitis, GB carcinoma, metastatic disease in the abdomen, lung cancer), many of whom were unable to consume 1.5 to 2.0 L of mannitol within the stipulated time of 45 to 60 minutes because of abdomen pain, vomiting, or diarrhea. Since patients with such diseases do not form the target population for CTC, in future studies where patients undergoing screening for colon cancer are evaluated, discomfort due to consumption of oral mannitol may be less, hence the technique of –SOP-CE-CTC can have better results than in our study. However, this is only our assumption. This technique may benefit many patients including the frail and elderly, who find the catharsis, instrumentation, and insufflation required for colonoscopy or CTC very distressing.

Nausea and vomiting is not a common occurrence with standard CTC using CO_2. Symptoms like nausea, vomiting (11%), abdomen pain (20%), and diarrhea experienced by some patients during SOP-CE-CTC may have been due to underlying diseases (such as pancreatitis, GB pathologies, and metastatic disease in the abdominal cavity), rather than due to consumption of large volume of mannitol. These can be medically managed more effectively in future studies with administration of antiemetics and buscopan, if necessary, before initiating oral mannitol. A postprocedural questionnaire may be used in future studies done for screening CRC, to assess patient discomfort/acceptance for SOP-CE-CTC.
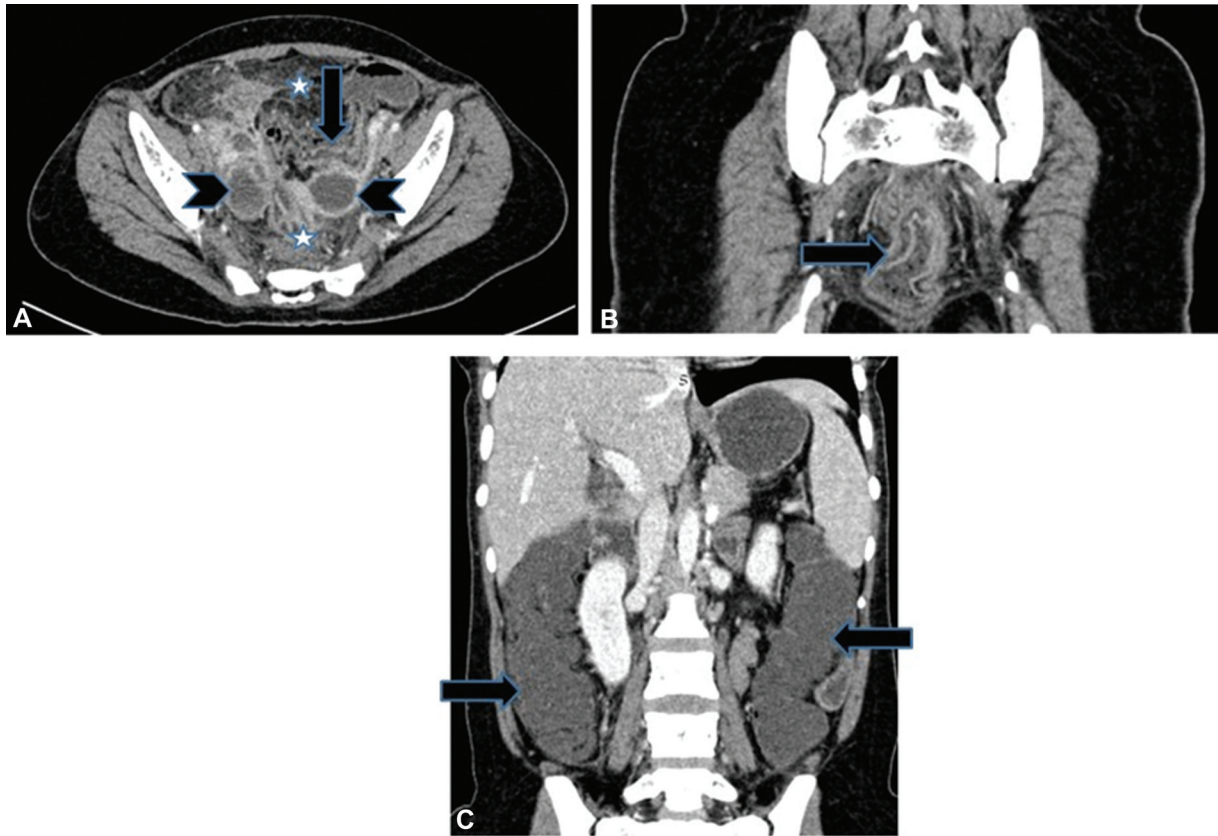
Fig. 10 A 22-year-old female showing (**A**) bilateral tubo-ovarian abscesses (arrowheads) with score 1 assigned to sigmoid colon (arrow) and (**B**) rectum (arrow). There was significant mural thickening of rectum and sigmoid colon with surrounding inflammatory changes in pelvis [white stars ** in (**A**)] which may be responsible for the rectosigmoid collapse. (**C**) Rest of the colonic segments showed optimal distension (arrows).

Another limitation of the study was that mural and mucosal fold visualization in the rectosigmoid was compromised due to the presence of fecal matter in 50 cases in the rectum and 33 cases in the sigmoid colon. For improving evaluation of the rectosigmoid colon, patients should be advised a liquid diet on the day before SOP-CE-CTC to reduce fecal residue, and oral bowel preparation can also be supplemented with local suppositories, in the future. Prone/decubitus position may be used in selected patients to mobilize the adherent fecal matter. Thus, in the majority of patients radiation dosage in SOP-CE-CTC will be at least half that of CTC, wherein scans are usually acquired in both prone and supine positions.

Despite suboptimal distension of some segments of the colon, compromised mucosal and mural visualization in the rectosigmoid due to fecal residue and discomfort reported during SOP-CE-CTC in some patients, we believe these shortcomings would be significantly less in the population undergoing screening for CRC with SOP-CE-CTC. In conclusion, –SOP-CE-CTC is a novel technique to achieve excellent colonic distension, wall delineation, and mucosal fold visualization using 3% oral mannitol solution and mild bowel preparation. Although the present technique has not been compared with the standard CTC, future exploration of SOP-CE-CTC for screening CRC should be undertaken.

Conflict of Interest
None declared.

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