Laxative-free CT colonography

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Objectives: The aim of this study was to determine if the introduction of faecal tagging to CT colonography (CTC) made the examination easier to tolerate or reduced the number of false-positives.

Methods: Our department changed bowel preparation for CT colonography from Picolax (Ferring Pharmaceuticals Ltd, London, UK) to Gastrografin® (Bracco Diagnostics Inc, Princeton, NJ) only with a modified diet. Questionnaires were given to a subgroup of patients within these cohorts. The numbers of false-positives were compared between two cohorts before and after this change. false-positives were defined as lesions reported on CT that were not confirmed by subsequent endoscopic examination. Polyps were matched if they were in the same or adjacent segments, and were within 5 mm of the reported size.

Results: 412 patients were identified from the Picolax cohort, and 116 from the Gastrografin cohort. 62 patients in each group completed questionnaires. Gastrografin produced less diarrhoea; 34% had five or more bowel motions in the previous day and night, compared with 77% for Picolax ($p < 0.001$), although more patients found drinking it unpleasant compared with Picolax (85% reported drinking Picolax as "easy" vs 61% for Gastrografin; $p = 0.002$). Picolax produced more non-diagnostic examinations, although this difference was not statistically significant. There was not a significant reduction in the numbers of false-positives (2 out of 112 for Gastrografin group, 14 out of 389 for the Picolax group; $p = 0.54$).

Conclusion: Switching from Picolax to Gastrografin as a CTC preparation technique produced less diarrhoea, but did not reduce the number of false-positives.

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Introduction

The UK National Health Service (NHS) National Patient Safety Agency (NPSA) has recently issued guidelines about how laxative bowel preparations commonly used for CT colonography (CTC) can be prescribed to patients [1]. These were based upon reported incidents of harm from use of these drugs, including one death. It is no longer acceptable for radiology departments to send patients laxative bowel preparation in the post based upon the very limited clinical information usually available on a radiology request card. This has made the process of organising CT colonography more cumbersome in our department. Several authors have described using faecal tagging, usually with diatrizoate dimeglumine (Gastrografin®; Bracco Diagnostics Inc, Princeton, NJ) in addition to laxatives, and a few have used Gastrografin on its own without any laxatives. We therefore undertook to change our preparation for CTC from sodium picosulphate (Picolax; Ferring Pharmaceuticals Ltd, London, UK) without faecal tagging to oral Gastrografin only, with no laxatives. We have compared patient acceptance before and after this change using a questionnaire. We do not have a reference test for all patients to give the true incidence of colonic neoplasia, so are unable to calculate sensitivity and specificity, but can calculate true- and false-positive rates based upon the results of further

investigations, principally optical colonoscopy, triggered by CTC reports. It has been proposed previously that faecal tagging can reduce the numbers of false-positives by enabling residual faeces to be more easily distinguished from true pathology. Previous studies have not shown this, but these have been small. We therefore sought to compare the false-positive rates between tagged and untagged groups, to see if faecal tagging reduces this number.

Methods and materials

This study was approved by the local ethics committee. Consecutive patients were identified from before and after the change in bowel preparation. Patients in the Picolax group were asked to take two sachets of Picolax the day before the examination as per the manufacturer's instruction leaflet [2]. Diet was also modified according to these instructions. For the Gastrografin preparation group, patients took 35 ml of Gastrografin mixed with a glass of water at 8pm 2 days before the CT, and another 35 ml at 8pm 1 day before. Two glass bottles, each containing 35 ml of Gastrografin and made in our pharmacy, were posted to patients in a padded envelope. Diet was modified to avoid high-fibre foods. The diet sheet given is in Appendix A. 40 min before the CT, patients were asked to drink our department's standard oral contrast: 15 ml of Urografin® (Bayer plc, Newbury, UK) 370 in 750 ml of tap water.

The CT examination was performed identically for the two groups, using a LightSpeed® VCT scanner

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(GE Healthcare, Little Chalfont, UK) at 120 kV, with a variable tube current. A mechanical insufflator was used to introduce carbon dioxide after intravenous injection of 20 mg of hyoscine butylbromide. Prone and supine series were acquired at 0.625-mm slice thickness. Intravenous contrast was not routinely used. Images were analysed using combined two- and three-dimensional analysis using either Vitrea® (Vital Images, Minnetonka, MN) or VCAR (GE Healthcare) workstations.

Questionnaires were given to patients attending for CTC as they arrived in the radiology department for their examination. These were modified from a previous study by Taylor et al [3]. Patients completed the questionnaires while they waited for their CT examination. The results were compared between the two groups. Results were compared using Fisher's exact test.

All were reported by consultant radiologists with experience of ≥ 200 CTC examinations at the beginning of the study period. Reports were classified as either normal or abnormal warranting endoscopic evaluation of a potential colonic abnormality >10 mm. Correlation with subsequent endoscopic and pathological reports was made, and reported abnormalities were classified as "true-positive", "false-positive" or "insufficient information for evaluation". The last were excluded from further analysis. When comparison with endoscopic examination was made, polyps were matched if they were in the same or adjacent segments and were within 5 mm of the reported size.

The outcome measure used for statistical analysis was whether there was a false-positive or not, considered to be a binary outcome. Owing to the nature of this outcome, Fisher's exact test was used to compare between scan methods. This method was preferred to the χ^2 test because of the relatively small number of false-positive results. Two sets of analyses were performed. For the first set all subjects who had a result other than false-positive were combined together into the "not false-positive" group. However, it could be argued that the true-positives could not have a false-positive result, so the analysis was repeated omitting the true-positives.

Results

62 patients in each group were given questionnaires. Results of the questionnaire are seen in Table 1. Results were compared using Fisher's exact test. Where numbers were very small, groups were added together for the purpose of statistical analysis. The main differences are in frequency of bowel movements, with Picolax causing 77% to have five or more bowel motions in the previous day and night, compared with 34% for Gastrografin ($p<0.001$). This was reflected in perianal soreness, which was experienced in 63% of patients receiving Picolax against 26% for Gastrografin ($p<0.001$). Patients preferred the experience of drinking Picolax compared with Gastrografin (reported as "easy" for 85% with Picolax *vs* 61% for Gastrografin; $p=0.002$).

A total of 116 patients were identified in the Gastrografin preparation group. 47% were male; age ranged from 42 to 84 years, with a mean of 63.5 years. Four patients were excluded. One patient was excluded

from statistical analysis because pathology identified was already known from an endoscopy before the CTC was performed; CTC was being used to evaluate the colon proximal to this. One patient was correctly reported as having Crohn's colitis, and another as having a diverticular abscess. These patients were excluded, as was a patient who had a 10-mm polyp reported, but was deemed unfit for colonoscopic examination to determine if this was correctly reported. This left 112 patients. Of these, nine were correctly reported as having colon cancer (true-positive). A benign 2-cm polyp was correctly reported. There was one false-positive diagnosis of malignancy. Endoscopy showed this to be a diverticular stricture. There was one false-positive diagnosis of a 10-mm polyp. No examinations were considered non-diagnostic.

A total of 412 patients were identified in the Picolax preparation group. 67% were male, and age ranged from 44 to 80 years, with a mean of 65.4 years. 15 were excluded owing to inadequate follow-up information, leaving 397. There were 14 false-positive lesions reported as being 10 mm or greater. There were 12 true-positive cancers and 16 true-positive large polyps. Eight were reported as non-diagnostic owing to excessive amounts of retained faecal residue.

The positive predictive values for lesions >10 mm for the Picolax and Gastrografin groups were 67% and 83%, respectively. Fisher's exact test was used to compare the occurrence of false-positives between CT methods; a summary of the results is given in Table 2. The figures reported are the number and percentage of patients with and without a false-positive for each of the two methods. The p -values indicate the significance of the differences between the two groups. The results indicated that there was no evidence of a statistically significant difference between the two methods for either of the two analyses. Although the results are not statistically different from each other, the false-positive rate was almost twice as large in the Picolax group.

A typical image obtained from the Gastrografin regimen is shown in Figure 1.

Discussion

The NPSA report into bowel cleansing agents [4] instructed British NHS trusts that safeguards should be implemented at a local level to reduce this risk, and specifically required that all trusts ensure that a clinical assessment of each patient for contraindications and risks occurs; that the use of a bowel cleansing preparation is authorised by a clinician; that an explanation on the safe use of the preparation is provided to the patient; and that a safe system exists for the supply of the preparation for each patient. This has made organisation of CTC services more difficult for our department. We had been considering using a form of faecal tagging for CTC, and because of the complexities introduced into prescription of Picolax we decided to use a regimen that did not use laxatives.

As CT examinations that were reported as normal did not have any further investigations, we do not have a true "reference" standard, and sensitivities and specificities cannot be calculated. We have calculated true- and false-positive rates based upon the results of further

Table 1. Results of the questionnaire: *n* (%)

I found understanding the instruction sheet		
	Picolax	Gastrografin
Easy	55 (89)	43 (69)
Fairly easy	5 (8)	19 (31)
Quite difficult	2 (3)	0 (0)
Very difficult	0 (0)	0 (0)
<i>p</i> =0.002		
I found swallowing the preparation medicine		
	Picolax	Gastrografin
Easy	53 (85)	38 (61)
Fairly easy	9 (14)	19 (31)
Quite difficult	0 (0)	4 (6)
Very difficult	0 (0)	1 (2)
<i>p</i> =0.002		
Coping with the special diet was		
	Picolax	Gastrografin
No problem	48 (77)	46 (74)
A bit difficult	14 (23)	16 (26)
Very difficult	0 (0)	0 (0)
Couldn't manage	0 (0)	0 (0)
Difference not significant <i>p</i> =0.83		
Regarding how you felt after the medicine		
	Picolax	Gastrografin
I felt fine	50 (81)	49 (79)
I felt unwell	10 (16)	9 (14)
I felt very unwell	2 (3)	4 (6)
Difference not significant <i>p</i> =0.78		
During all of the day and night before the CT, how many times did you open your bowels?		
	Picolax	Gastrografin
Nil	0 (0)	5 (8)
Once	1 (2)	11 (18)
Two to four times	13 (21)	25 (40)
Five or more times	48 (77)	21 (34)
<i>p</i> <0.001		
Did you experience any abdominal cramps or pain?		
	Picolax	Gastrografin
None	29 (47)	38 (61)
Mild	25 (40)	19 (31)
Moderate	8 (13)	4 (6)
Severe	0 (0)	1 (2)
Difference not significant <i>p</i> =0.24		
Did you experience nausea or vomiting?		
	Picolax	Gastrografin
None	49 (79)	45 (73)
Mild	13 (21)	15 (24)
Moderate	0 (0)	2 (3)
Severe	0 (0)	0 (0)
Difference not significant <i>p</i> =0.40		

Table 1. Continued

Did you experience any faintness or dizziness?		
	Picolax	Gastrografin
None	47 (76)	51 (82)
Mild	14 (23)	10 (16)
Moderate	1 (2)	1 (2)
Severe	0 (0)	0 (0)
Difference not significant <i>p</i> =0.51		
Did you experience any wind?		
	Picolax	Gastrografin
None	20 (32)	15 (24)
Mild	35 (56)	28 (45)
Moderate	6 (10)	14 (23)
Severe	1 (2)	5 (8)
Difference not significant <i>p</i> =0.07		
Did you experience any soreness?		
	Picolax	Gastrografin
None	22 (35)	46 (74)
Mild	32 (52)	10 (16)
Moderate	5 (8)	5 (8)
Severe	2 (3)	1 (2)
<i>p</i> <0.001		
Did you experience any incontinence/accidents?		
	Picolax	Gastrografin
None	50 (81)	56 (90)
Mild	6 (10)	2 (3)
Moderate	4 (6)	3 (5)
Severe	2 (3)	1 (2)
Difference not significant <i>p</i> =0.44		
Did you experience any sleep disturbance?		
	Picolax	Gastrografin
None	34 (55)	39 (63)
Mild	17 (27)	13 (21)
Moderate	7 (11)	6 (10)
Severe	4 (6)	4 (6)
Difference not significant <i>p</i> =0.81		

Bold indicates significant levels <0.05.

investigations triggered by CTC reports. There was no statistically significant difference in numbers of false-positives. Despite the large sample size, the study is relatively underpowered to show this sort of difference as statistically significant. This is because of the rarity of false-positive results. It can be calculated that (with a 5% significance level and 80% power) the numbers would have had to be >1200 per CT method in order to detect this sort of difference as statistically significant. Therefore, it is perhaps not surprising that no difference was found for these data.

Gastrografin was well tolerated as a preparation, producing less diarrhoea, although patients found that swallowing Gastrografin more unpleasant than

Table 2. Results of numbers of false-positives between Gastrografin preparation and Picolax preparation groups

Analysis	Result	Gastrografin number (%)	Picolax number (%)	p-value
All subjects	Not false-positive	110 (98.2)	375 (96.4)	0.54
	False-positive	2 (1.8)	14 (3.6)	
Omitting true-positives	Not false-positive	100 (98.0)	347 (96.1)	0.54
	False-positive	2 (2.0)	14 (3.9)	

drinking Picolax, probably owing to the strong aniseed flavour of Gastrografin. There was a difference in the number of studies considered non-diagnostic (eight in the Picolax group *vs* none in the Gastrografin group), although this difference was not statistically significant.

Faecal tagging combined with laxatives is well described, most notably by Pickhardt et al [5]. However, hard evidence of benefit in sensitivity or specificity is lacking. It has been suggested previously that use of faecal tagging would reduce the number of false-positives because small amounts of residual faecal material would be more easily distinguished from true pathology. However, previous studies have not shown this. Lefere et al [6] found a non-significant increase in specificity when a polyethylene glycol (PEG) regimen was compared with a single dose of magnesium citrate combined with barium tagging. Fletcher et al [7] randomly assigned 180 patients to have conventional bowel preparation (PEG in this case) or bowel preparation plus faecal tagging consisting of 120 ml of Gastrografin the night before the examination. Sensitivity and specificity for polyp detection were not changed, but the authors commented that the tagging regimen did not work very well (only 48% showed a measurable increase in the attenuation of colonic fluid). Clearly this is a reasonable dose of Gastrografin, higher than we have used, and it is not clear why this did not work. Perhaps the PEG

preparation, which leaves a high volume of fluid in the colon, washed out the Gastrografin.

The first report of the use of iodinated contrast alone without laxatives was by Iannaccone et al [8]. They described use of Gastrografin taken with a low-fibre diet at a dose of 100 ml per day for 2 days before CT. This resulted in excellent tagging with good sensitivity for pathology compared with subsequent colonoscopy. The reference colonoscopy used standard laxative preparation and patients reported preferring the Gastrografin technique. Our anecdotal experience was that even 100 ml of Gastrografin caused significant diarrhoea, so a lower dose was chosen for this study.

Campanella et al [9] described results of CTC in three different groups: (1) high-dose phopha soda with 100 ml of Gastrografin over 2 days, (2) a mild "laxative" (macrogol) with 50 ml of Gastrografin 2 h before the exam and (3) 2 ml kg⁻¹ Gastrografin over 2 days without laxatives. All patients were asked to comply with a low-fibre diet for 2 days before the exam, and to fast on the day. The third group is similar to our preparation regimen, although they did not use oral contrast immediately before the examination. They assessed the quality of tagging both qualitatively and quantitatively, and found that the third group (Gastrografin alone) performed the worst. Patient acceptance was rated, with the first group describing a significantly worse experience. They concluded that the second group provided the best compromise between tagging quality and patient acceptance.

Liedenbaum et al [10] report use of CTC without laxatives with iodine tagging only. They used meglumine ioxithalamate (Telebrix) in a dose of 50 ml three times per day over 2 days for the first 50 patients, and 3 × 50 ml in 1 day for the next 50. A low-fibre diet was used for both groups, together with 50 ml of Telebrix 1.5 h before the examination. A reference standard of subsequent colonoscopy was used to assess accuracy of pathology detection, quality of tagging was graded and patient symptoms were evaluated. They reported that image quality and polyp detection were comparable between the two regimens, but the 1-day preparation group had less diarrhoea.

Johnson et al [11] report good results with barium faecal tagging with no diet modification or laxatives, in particular a high specificity (100%) for large adenomas. This is surprising, and other studies using this technique have produced poor results [12]. This is likely to be due to the insolubility of barium and its tendency to accumulate at the base of pools of fluid. Most practitioners using barium tagging would combine it with at least a reduced dose of laxatives [13]. Taylor et al [3] reported a reduced laxative CTC regimen using barium-based tagging. This was tolerated better than full laxative bowel preparation and produced results comparable to

Figure 1. A typical CT colonography image obtained from the Gastrografin® (Bracco Diagnostics Inc, Princeton, NJ) preparation regimen. The colon is well distended and contains a small amount of homogeneously tagged fluid.

conventional-preparation CTC. Nagata et al [14] compared barium-based and iodine-based tagging regimens and found that the latter produced more homogeneity and a high attenuation in the tagged faecal material.

Minimal-preparation CT colon is a technique related to CTC that uses Gastrografin faecal tagging at a low dose of 10 ml per day without laxatives, diet modification or gas insufflation [15]. No studies have documented whether this dose causes diarrhoea, but as this is advocated as a test for the frail elderly it is reasonable to assume that any diarrhoea caused is mild. It is clear from our results that Gastrografin at a higher dose of 35 ml per day does cause some diarrhoea, and therefore that Gastrografin is itself a laxative. However, the effects are less severe than those of Picolax.

Allergic reactions to iodinated contrast occur. None was recorded in this study group, but anecdotally we have noted occasional skin rashes after Gastrografin ingestion. At our department we have posted Gastrografin to patients to drink at home for 10 years and are not aware of any more serious reactions.

There are several limitations with this study. Clearly randomising patients to tagging regimen or standard regimen would have been preferable. In retrospect it is clear that our sample size was too small to demonstrate a reduction in false-positives, but the sample needed of 1200 per method would have been difficult to achieve. An alternative strategy would be to use a polyp-enriched population. We did not formally grade the quality of tagging achieved, but none of the tagged data set was considered non-diagnostic. Although all reporting radiologists were experienced in CTC, further experience gained during the study could have affected the reporting accuracy of the two groups. This would favour the Gastrografin preparation group, which was reported second.

Conclusion

We have described a simple bowel preparation technique that does not use laxatives, thus bypassing NPSA regulations. This regimen is well tolerated, inducing less diarrhoea than conventional laxative-based techniques, although care must still be taken in prescribing as diarrhoea still occurs, and it should be avoided in those with an iodine allergy. We have not shown that use of faecal tagging reduces false-positives. Use of mild laxatives not covered by NPSA guidelines may improve the quality of tagging, but at the expense of increased complexity of the regimen.

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References

1. NPSA. Reducing risk of harm from oral bowel cleansing solutions. National Patient Safety Agency alert issued 19 February 2009. [cited 18 November 2011]. Available from: www.nrls.npsa.nhs.uk/alerts/?entryid45=59869&p=2
2. Picolax. Patient information leaflet. [cited 18 November 2011]. Available from: <http://www.medicines.org.uk/EMC/medicine/18010/PIL/Picolax>
3. Taylor SA, Slater A, Burling DN, Tam E, Greenhalgh R, Gartner L, et al. CT colonography: optimisation, diagnostic performance and patient acceptability of reduced-laxative regimens using barium-based faecal tagging. *Eur Radiol* 2008;18:32–42.
4. Royal College of Radiologists. Consensus Guidelines for the Prescription and Administration of Oral Bowel Cleansing Agents. [cited 18 November 2011]. Available from: www.rcr.ac.uk/publications.aspx?PageID=310&PublicationID=309
5. Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003;349:2191–200.
6. Lefere PA, Gryspeerdt SS, Dewyspelaere J, Baekelandt M, Van Holsbeeck BG. Dietary fecal tagging as a cleansing method before CT colonography: initial results polyp detection and patient acceptance. *Radiology* 2002;224:393–403.
7. Fletcher JG, Johnson CD, Welch TJ, MacCarty RL, Ahlquist DA, Reed JE, et al. Optimization of CT colonography technique: prospective trial in 180 patients. *Radiology* 2000;216:704–11.
8. Iannaccone R, Laghi A, Catalano C, Mangiapane F, Lamazza A, Schillaci A, et al. Computed tomographic colonography without cathartic preparation for the detection of colorectal polyps. *Gastroenterology* 2004;127:1300–11.
9. Campanella D, Morra L, Delsanto S, Tartaglia V, Asnaghi R, Bert A, et al. Comparison of three different iodine-based bowel regimens for CT colonography. *Eur Radiol* 2010;20:348–58.
10. Liedenbaum MH, de Vries AH, Gouw CI, van Rijn AF, Bipat S, Dekker E, et al. CT colonography with minimal bowel preparation: evaluation of tagging quality, patient acceptance and diagnostic accuracy in two iodine-based preparation schemes. *Eur Radiol* 2010;20:367–76.
11. Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008;359:1207–17.
12. Zalis ME, Perumpillichira JJ, Magee C, Kohlberg G, Hahn PF. Tagging-based, electronically cleansed CT colonography: evaluation of patient comfort and image readability. *Radiology* 2006;239:149–59.
13. Kim MJ, Park SH, Lee SS, Byeon JS, Choi EK, Kim JH, et al. Efficacy of barium-based fecal tagging for CT colonography: a comparison between the use of high and low density barium suspensions in a Korean population: a preliminary study. *Korean J Radiol* 2009;10:25–33.
14. Nagata K, Singh AK, Sangwaiya MJ, Näppi J, Zalis ME, Cai W, et al. Comparative evaluation of the fecal-tagging quality in CT colonography: barium vs. iodinated oral contrast agent. *Acad Radiol* 2009;16:1393–9.
15. Ganeshan A, Upponi S, Uberoi R, D'Costa H, Picking C, Bungay H. Minimal-preparation CT colon in detection of colonic cancer, the Oxford experience. *Age Ageing* 2007;36:48–52.

Appendix A

Diet sheet for Gastrografin group

Diet sheet to be followed for 2 days before the CT scan

What you eat will improve the performance of the bowel preparation and enhance the diagnostic accuracy of the procedure. Please select foods from the allowed list below. A suggested menu is given at the bottom of the page.

	Allowed	Please avoid
Dairy	Limited to 2 cups Use low fat products; milk, plain yogurt	Yogurt with fruit skins or seeds; strongly flavoured cheeses
Meat	Plainly prepared; white fish, poultry, eggs	Red meat (pork, beef), added fats, gravies, fried sauces, heavy seasonings, oily fish
Potato/pasta/vegetables	White rice, spaghetti, noodles/macaroni, potato with no skin	Potato with skin, brown rice, all other vegetables
Bread/cereal	White (refined) breads, crackers, cooked rice	Whole grain (bran, cornmeal) breads, whole grain crackers and cereals, popcorn
Fruit/fruit juices	Clear fruit juices, canned fruit (no seeds or skin)	Raw fruits, raisins, dried fruits, prunes/prune juice, skins
Beverages	Coffee or tea limited to two cups per day, carbonated drinks, water, fruit flavoured drinks	All others
Soup	Bouillon (clear soup)/broth	All other
Dessert	Gelatin, fruit ice, popsicle	Coconut, nuts, seeds, hard clear candies, fruits that are not allowed on this list
Miscellaneous	Salt, pepper, jelly, sugar, honey, syrup	Cloves, garlic, seed spices, chilli sauce, barbecue sauce, any strongly flavoured spice or sauce, mustard, jam, marmalade, peanut butter

Suggested menu for 2 days before the CT scan

Breakfast	Lunch	Dinner
Plain yogurt	Soup	Soup
Refined bread/toast, but without marmalade or jam	White fish/chicken	White fish/chicken
Eggs	White rice	White rice, pasta or potato
Clear fruit juice	Bread/cracker	Bread/cracker
	Dessert/fruit	Dessert/fruit