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Original Investigation

Estimated GFR Decline Following Sodium Phosphate Enemas Versus Polyethylene Glycol for Screening Colonoscopy: A Retrospective Cohort Study

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Background: Associations between sodium phosphate enemas and nephropathy have raised concerns about the safety of use as part of a bowel-cleansing regimen administered prior to colonoscopies. The objectives of this analysis are to evaluate the impact of sodium phosphate enema versus polyethylene glycol powder for oral solution (PEG) use prior to colonoscopy screening on estimated glomerular filtration rate (eGFR) decline in Veterans Affairs (VA) patients and identify other risk factors contributing to eGFR decline.

Study Design: Retrospective cohort study.

Setting & Participants: 70,499 VA patients receiving sodium phosphate enemas (with or without PEG) or PEG alone prior to colonoscopy screenings.

Predictor: Use of either sodium phosphate or PEG.

Outcomes: A 50% increase in serum creatinine level over a 15-month, over a 6-week, and between a 9- and 15-month period was used to define any, acute, or long-term eGFR decline, respectively.

Measurements: Multivariable logistic regressions estimated the likelihood of eGFR decline conditional on the use of sodium phosphate enemas versus PEG alone, controlling for potential confounders.

Results: A greater proportion of patients using sodium phosphate enemas versus PEG had any ($P < 0.001$) or long-term ($P = 0.003$) eGFR declines, whereas similar proportions had acute eGFR declines ($P = 0.9$). In the adjusted analyses, use of sodium phosphate enemas (± PEG was associated with an increased likelihood of having any (OR, 1.3; 95% CI, 1.2-1.5) or long-term (OR, 1.4; 95% CI, 1.1-1.8) eGFR decline, but not acute eGFR decline (OR, 1.0; 95% CI, 0.6-1.7). Other risk factors for eGFR decline included diabetes and non–iron deficient anemia.

Limitations: Unobserved heterogeneity due to volume depletion and potential selection bias due to higher-risk patients preferentially prescribed sodium phosphate enemas.

Conclusions: Use of sodium phosphate enemas versus PEG alone prior to colonoscopy screening increases the risk for VA patients having long-term eGFR decline. Patients with non–iron deficient anemia are at particularly high risk for eGFR decline. These findings motivate the need to re-examine prescribing practices for sodium phosphate enemas as part of a bowel-cleansing regimen.

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INDEX WORDS: Polyethylene glycol (PEG); sodium phosphate enema; bowel cleansing; bowel purgative preparation; veterans; colonoscopy; estimated glomerular filtration rate (eGFR); eGFR decline; renal function; nephropathy; risk factor.

The nephrotoxic effect of phosphate-containing cathartic preparations has gained recognition. The use of oral phosphate-containing preparations (oral sodium phosphates [OSPs]) for bowel cleansing prior to colonoscopy gained popularity in the 1990s because compared with polyethylene glycol (PEG) preparations, OSP preparations were better tolerated and more effective[1,2] and produced better quality cleansing.[3] However, initial case studies showing associations between OSP administration and reduced kidney function prompted the US Food and Drug Administration (FDA) to issue black box warnings,[4] followed by an alert in 2008 advising that over-the-counter OSP products no longer be used for bowel cleansing without a prescription.[5]

The concern about OSPs causing nephropathy is well justified based on results of retrospective cohort,[6-8] retrospective case-control,[3] and case-crossover studies[9] showing evidence of kidney injury following OSP administration. These results are corroborated with biopsies showing histologic changes of nephrocalcinosis in those administered OSPs prior to colonoscopy screenings.[10,11] In one case study, biopsy

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findings included signs of tubular necrosis, as well as deposits containing phosphate and calcium ions that were postulated to have led to obstructive lesions resulting in tubular necrosis and chronic renal impairment.[11] Despite evidence of the dangers of OSPs, sodium phosphate enemas remain available in the US market and continue to be used as part of bowel-cleansing regimens precolonoscopy. The potential for adverse events following sodium phosphate enema use as part of a bowel-cleansing regimen is not fully understood and is under-recognized by health care providers. Numerous case reports have surfaced in the recent past linking sodium phosphate enemas to kidney damage.[12-14] In one case, calcium-phosphate deposition in the renal tubular lumens was seen on autopsy after a death secondary to presumed acute kidney failure following sodium phosphate enema administration for constipation.[12] As the number of these reports grows, so does the concern that sodium phosphate enema administration may produce kidney injury from significant absorption of phosphate, analogous to OSPs.

The increased risk for OSP-induced nephropathy in older populations[7] and the suggestion of risk for kidney injury with sodium phosphate enemas based on case reports motivates the need to evaluate the impact of administering sodium phosphate enemas as part of a bowel-cleansing regimen on kidney injury among US Department of Veterans Affairs (VA) patients receiving colonoscopy screenings. Studying these within the framework of a cohort study with a large sample size in contrast to a randomized trial with smaller sample sizes will be better suited to determine clinical safety, especially within the context of rare outcomes. Because the incidence of sodium phosphate enema–related nephropathy is not as well characterized as OSP-related nephropathy, the associated risks are not recognized by providers who prescribe sodium phosphate enemas.

Our primary objective was to evaluate the extent to which sodium phosphate enemas are associated with estimated glomerular filtration rate (eGFR) decline within a VA population. We accomplished this objective by estimating the risk for patients having any eGFR decline, acute eGFR decline, and long-term eGFR decline within VA patients being administered sodium phosphate enemas as part of a bowel-cleansing regimen versus PEG bowel purgatives in preparation for colonoscopy screenings. Our secondary objective was to identify the significant risk factors independent of bowel purgative preparations that are associated with kidney functioning by estimating the risk for eGFR decline conditional on known risk factors for kidney disease or kidney injury. We hypothesize that screening colonoscopy patients exposed to sodium phosphate enema products will have an increased likelihood of eGFR decline compared with those exposed to alternative laxatives.

METHODS

This retrospective observational cohort study used administrative claims data extracted from the VA Corporate Data Warehouse containing data for all VA beneficiaries January 1, 2000, to September 30, 2011. Patients were included in the cohort if they: (1) underwent a colonoscopy screening during January 1, 2002, to June 30, 2011, as indicated by a combination of both a *Current Procedural Terminology* (*CPT*) code (45378-45392, G0105, or G0121) and a primary diagnosis *International Classification of Diseases, Ninth Revision* (*ICD-9*) code (V76.41 or V76.51); (2) had at least 2 years of baseline data prior to their index colonoscopy screening; and (3) had at least 15 months of follow-up time post–index colonoscopy screening in order to collect laboratory values. To be included in the analysis, patients also had to have evidence of being issued at least 1 VA prescription for a sodium phosphate enema or PEG bowel-cleansing purgative as indicated by the drug name fields within the pharmacy claims data within a 6-month period prior to the index colonoscopy screening. Six months was selected because bowel preparation prescriptions for sodium phosphate enemas and PEG are sometimes processed at the time the colonoscopy procedure is ordered, which may not be scheduled for several weeks or months after. Furthermore, patients had to have 1 or more serum creatinine laboratory value and laboratory test date available within the 1 year prior to the index colonoscopy screening in addition to 1 or more serum creatinine value and laboratory test date available within the 15 months following the screening colonoscopy.

Because some patients receive colonoscopies for diagnostic rather than screening purposes, using only *CPT* codes as inclusion criteria is likely not sufficient. Therefore, to ensure that only those receiving screening colonoscopies as opposed to diagnostic colonoscopies were included in the analysis, we excluded VA patients: (1) younger than 50 years, (2) having undergone 1 or more colonoscopy within the 1 year prior to the date of the screening colonoscopy, or (3) having a primary diagnosis of iron deficiency, unspecified anemia, ulcerative colitis, diverticulosis, gastrointestinal hemorrhage, blood in stool, or symptom (700-799) associated with the colonoscopy visit (Fig 1). The rationale for these criteria was as follows. First, patients undergoing colonoscopy at younger than 50 years are at high risk for malignancy or have further indication for colonoscopy. Second, patients with multiple colonoscopies are likely undergoing these for diagnostic purposes, not screening, and are likely to be high risk as well. Third, patients with these primary diagnoses listed are more likely to be receiving a colonoscopy for diagnostic rather than screening purposes.

We further excluded VA patients who within 2 years prior to screening colonoscopy: (1) were older than 90 years on the index date of the colonoscopy screening; (2) had a diagnosis of malignant neoplasm, dementia, heart failure, or liver disease or were receiving dialysis; (3) had an inpatient admission within the 3 months prior to colonoscopy; (4) had proteinuria with protein excretion > 3.5 g/d, protein-creatinine ratio > 3.5 g, or diagnosis of nephropathy; (5) had chronic kidney disease (CKD) stage 5 as defined by a threshold of eGFR < 15 mL/min/1.73 m^2 as calculated using the isotope-dilution mass spectrometry–traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation (we assumed that all participants were non–African American because data for race were very limited); (6) were exposed to intravenous contrast within 7 days prior to the index date of the colonoscopy screening; or (7) received a prescription for oral phosphate products in the 6 months prior to the index date of the colonoscopy screening (Fig 1). Excluding patients with nephrotic-range proteinuria based on protein-creatinine ratio