EDITORIAL

Bowel preparation for colonoscopy and hypokalemia: at the heart of the problem!

Colonoscopy has quickly become the preferred primary test for colorectal cancer (CRC) screening in the United States,[1] and it is also extensively used for the same indication or similar indications (ie, workup after a positive fecal test result) in Europe.[2] The success of colonoscopy is mainly explained by its high accuracy in detecting (advanced) neoplasia, which in turn has been related to a remarkable degree of CRC incidence and mortality prevention.[3,4] In addition, the strict association between quality of the colonoscopy and the risk of postcolonoscopy cancer has prompted strategies to maximize the performance of the endoscopist in terms of detection, to minimize the risk of postcolonoscopy interval cancer.[5,6]

No doubt, colonoscopy is by far the most effective test for preventing CRC, but what about its safety?

When a preventive technique is implemented at the population level, safety remains an inescapable prerequisite. Any significant risk of morbidity associated with colonoscopy would severely undermine its risk/benefit profile. The safety of colonoscopy has been mainly addressed by estimating the risk of bleeding or perforation during diagnostic and operative procedures,[7] leading to the persuasive conviction that its main risks are merely related to its technical aspects. However, epidemiologic surveys have shown unexpected—albeit small—risks of cardiovascular or other non-GI events, especially in elderly patients or those with comorbidities.[8-10]

If the high safety of colonoscopy is a prerequisite for its widespread implementation, a major pillar is represented by the safety of bowel preparations based on polyethylene glycol (PEG).

Of the main steps forward in colonoscopy safety, the development of bowel preparations based on PEG remains by far the most relevant. PEG-based regimens have been purposely developed to allow a high flow of liquids to clean the colorectal mucosa without generating significant fluid and electrolyte shifts.[11] In particular, PEG solutions successfully minimize the loss of potassium because of their isotonic nature and the addition of an adequate supply of electrolytes.[12] Inasmuch as their superior safety was consistently shown in several studies,[13] PEG-based solutions have been widely recommended as preferred regimens not only for healthy individuals but also for those with clinically relevant comorbidities, such as cardiovascular or nephrologic diseases.[14,15] By contrast, non-PEG regimens are usually considered to result in higher rates of dehydration or electrolyte shifts, requiring special precautions, especially in high-risk patients.[14,15]

Have we become too confident about the safety of PEG? What if hypokalemia develops in some patients when PEG-based regimens are used?

These critical issues have been addressed in this issue of *Gastrointestinal Endoscopy* by Reumkens et al,[16] who prospectively assessed the prevalence of hypokalemia before and after a low-volume PEG-based preparation. By selecting a cohort of patients at high risk for hypokalemia, such as those receiving diuretic agents, those who are hospitalized, or those who experience chronic diarrhea, the authors showed a mild and moderate hypokalemia in 3.8% and 0.4% of the patients before bowel preparation, respectively, whereas no patient experienced severe hypokalemia.[16] By repeating the determination of potassium levels after PEG-based preparation in a subgroup of 301 hospitalized patients, the authors showed an unexpected 5-fold and 9-fold increase in the rates of mild and moderate hypokalemia, now occurring in 19.2% and 3.6% of patients, respectively.[16] In addition, severe hypokalemia was reported in 2 of 301 patients, corresponding to a 0.7% rate.[16]

> To minimize the risk of potentially serious adverse events, endoscopists should focus not only on risk factors directly related to the technique itself but also on those not directly related to colonoscopy, such as bowel preparation or anesthesiologist assistance.

On the basis of these data, should we strictly monitor potassium levels in patients at high risk for hypokalemia before and after PEG-based bowel preparations?

The feasibility and efficacy of any monitoring process would depend on 3 main variables: (1) the frequency of patients at high risk for hypokalemia, (2) the clinical relevance of hypokalemia, and (3) the efficacy of the corrective intervention.

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FREQUENCY OF HIGH-RISK PATIENTS

Previous studies have already shown a significant risk of hypokalemia after PEG-based bowel preparation in elderly patients, especially when they are hospitalized, have comorbidities, or receive diuretic therapy.[17,18] By using similar criteria (use of diuretics, hospitalization, or history of diarrhea or inflammatory bowel disease), Reumkens et al[16] estimated that 33% of all of the patients referred for colonoscopy would be categorized as being at high risk for hypokalemia. This is not unexpected when we consider that thiazide diuretic agents are frequently used for hypertension, which is highly prevalent in the colonoscopy population. These drugs deplete potassium by inhibiting chloride-dependent sodium resorption and inducing potassium excretion in a dose-dependent manner. At multivariate analysis, the authors were able to identify hospitalization and diuretic agents as independent predictors of hypokalemia before and after (only diuretic) bowel preparation.[16] These 2 criteria would restrict the high-risk population to approximately 16% of the initial colonoscopy population.[16] Of note, only 6% of the patients concomitantly presented with both of the risk factors, namely, hospitalization and use of diuretic agents.[16]

CLINICAL RELEVANCE OF HYPOKALEMIA

This is by far the most critical issue. The main aim of any monitoring for hypokalemia before and after bowel preparation should be to selectively identify those at significant morbidity related to the hypokalemic effect of bowel preparation, whereas the conversion of such monitoring for the detection of otherwise nonrelevant hypokalemia departs from the purpose of endoscopic activity, inasmuch as that should be the target for general practitioners or cardiologists. Intracellular and extracellular potassium concentrations are a major determinant of resting membrane potential difference. Hypokalemia determines cellular hyperpolarity, increases resting potential, accelerates depolarization, and increases automaticity and excitability. Through these mechanisms, hypokalemia increases the risk of ventricular arrhythmia and sudden cardiac death. Symptoms related to hypokalemia are usually poorly specific, requiring a special alert for their diagnosis. In general, mild hypokalemia is usually asymptomatic, but those with more pronounced decreases may experience muscle weakness, fatigue, and constipation, whereas severe hypokalemia ($\leq$2.5 mmol/L) may cause life-threatening cardiac arrhythmias and impaired respiration. Of interest, no hospitalization occurred among the 1332 normokalemic patients in the series by Reumkens et al,[16] even though we are now aware that a substantial proportion of them was likely to experience mild to moderate hypokalemia after bowel preparation, and we may guess that the threshold for the identification of hypokalemia-related symptoms and signs was quite low, inasmuch as the authors were aware of conducting a study on its clinical effects. This is probably explained by the fact that hypokalemia does not necessarily have clinical consequences.[19] First, the clinical relevance of hypokalemia is associated not only with its severity but also with the rapidity of its onset.[19] Given that most of the patients who became hypokalemic after bowel preparation were already receiving diuretic therapy, a gradual loss of intracellular potassium in at least some cases cannot be excluded[16] Second, the most severe clinical outcome of hypokalemia (ie, life-threatening arrhythmia) is uncommon in otherwise healthy individuals.[19] On the other hand, it is well documented that patients with congestive heart failure, ischemia, or a history of arrhythmia are at high risk for the development of life-threatening arrhythmia when they are hypokalemic, requiring a prompt reversal of the loss of potassium.[19] Of interest, the authors reported that the initial trigger for their research was represented by the occurrence of fatal arrhythmias in 2 patients, in whom the PEG-induced hypokalemia was only 1 of the factors contributing to death.[16] Similarly, a severe case of ventricular arrhythmia referred to PEG-induced hypokalemia occurred in a patient with severe left ventricular dysfunction and an automatic implantable cardioverter defibrillator.[20] In an old series of ventricular ectopy associated with PEG-based bowel preparation, older age and heart disease were significantly associated with such outcomes.[21] This was not unexpected, given that in heart failure, a condition in which 50% of deaths are sudden and most probably linked to fatal arrhythmias, hypokalemia is a strong predictor of mortality.

EFFICACY OF THE CORRECTIVE INTERVENTION

As reported by the authors, correction of mild to moderate hypokalemia requires only oral potassium supplementation, whereas intravenous treatment is reserved for those with severe hypokalemia.[16] These interventions have been presumably effective in preventing unfavorable outcomes in patients who were already hypokalemic before bowel preparation,[16] and endoscopists should be aware of them.

When all of these points are taken into consideration, a reasonable compromise between feasibility (ie, burden of serologic test) and safety may be (at least in theory) to grade patients who are at increased risk for hypokalemia after a PEG-based preparation according to the probability of an unfavorable outcome related to the hypokalemia itself, as shown in Table 1. Thus, potassium monitoring could be considered in patients at high risk for hypokalemia, such as those receiving diuretic therapy or who are hospitalized, when those patients are at the same time at high risk for a bad outcome from hypokalemia itself, such