Bowel preparation for colonoscopy : Efficacy, tolerability and safety

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Abstract

Adequate cleansing of the bowel is important for a reliable and diagnostic colonoscopy. Proper bowel preparation is directly correlated to the diagnostic performance of colonoscopy, procedure time, cost price and the complication rate. The ideal bowel preparation agent should be efficient, safe and well tolerated by the patient. Numerous agents have become commercially available overtime. Current agents can be classified according to their tonicity, as being isotonic or hypertonic. Poly-ethylene glycol based solutions balanced with electrolytes are the prototype of isotonic bowel preparations. Poly-ethylene solutions are safe and efficient in cleaning the bowel. Volume related side-effects are common, leading to innovations such as split dosing, and low volume solution combined with another laxative. Sodium phosphate and magnesium oxide are hypertonic agents. They are efficient and well tolerated, but safety issues regarding sodium phosphate has hampered its success. Because most physician are likely to prescribe bowel preparation agents for colonoscopy, they should be aware of the range of preparations commercially available and their limitations. This review focuses on the efficacy, tolerability and safety of current available bowel preparation agents. (Acta gastroenterol. belg., **2014**, 77, **249-255**).

Key words : bowel preparation, colonoscopy, safety, polyethylene glycol, sodium phosphate, magnesium oxide.

Introduction

Adequate bowel preparation is a major determinant of quality of colonoscopy. Colonoscopy is the preferred method of evaluation of the bowel for several indications. It is conceptually the best technique for visualizing the entire colonic mucosa and carries the possibility to preventively remove polyps (1,2). Over 14 million colonoscopies are performed annually in the US alone (3). These numbers are expected to increase because of the high number unscreened eligible persons in the population and the high capacity of endoscopic units (4). Because of the high demand for colonoscopies, adequate bowel preparation remains an important challenge (5,6,7). Adequate bowel preparation is directly correlated to important quality indicators such as polyp detection and caecal intubation rate. Additionally, a good bowel preparation is time saving and safer (8). Suboptimal bowel preparation occurs in 25% to 40% of cases (2). Several studies indicate that detection of polyps and neoplastic lesions depend greatly on the quality of bowel preparation (9-11). The quality of bowel preparation should therefore be documented because of the medical-legal risk of interval cancers after a suboptimal bowel prepared colonoscopy (12). Suboptimal bowel preparation is also associated with technical failure of colonoscopy. Up to 25% of incomplete colonoscopies are associated with poor bowel preparation (13). Resulting in higher cost due to increased duration of the procedure and need for repeat colonoscopy (6). Despite the importance of adequate bowel preparation not a single best agent for bowel cleansing has been identified (8). This review focuses on the efficacy, tolerability and safety of current colon cleansing agents.

Types of bowel preparations

Overtime numerous types of bowel preparations have become available. These are the result of continuous efforts to increase the efficacy, tolerability and safety of the cleansing agents. The ideal bowel preparation agent should indeed have an optimal efficacy in clearing the colon of residual stool without altering the mucosal morphology. It should also have an excellent patient tolerability with regards to palatability, side-effects (e.g. cramping, nausea…), price and safety. The latter is particularly important in elderly patients and patients with heart, liver and kidney disease (7,14,15). Strategies used for colon cleansing in colonoscopy have evolved from similar strategies of colon cleansing in surgical en radiological interventions (7). Dietary modification, cathartic agents (= agents that accelerated defecation) and enemas, used to be the cornerstone of bowel preparation. Typically a low residue diet with clear liquids was instituted one to three days before colonoscopy in adjunction with enemas and oral cathartics such as senna (6). These strategies are time consuming (two to three days) and significantly interfere with daily activities. Cathartics agents also generate fluid and electrolyte disturbances rendering them less preferable in patients with significant cardiac or renal co-morbidities (2,7). Dietary restriction alone is insufficient but is probably useful as an addition to current bowel cleansing strategies (16). Recent European Society of Gastrointestinal Endoscopy (ESGE) guidelines advise the institution of a low fiber diet the day preceding colonoscopy (5). The use of large volume (7 to 12 liters) saline gut lavages or mannitol based solution has also been relegated to a historical footnote

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Submission date : 28/12/2013
Acceptance date : 31/01/2014

because of poor patient tolerability and induction of fluid and electrolyte disturbances (6,7). Current cleansing agents are peroral solutions that have evolved from innovations in the 1980's, with the introduction of polyethylene glycol- electrolyte (PEG-E) solutions and sodium phosphate solutions (NaP) (7). In general, current agents can be classified according to their tonicity as being isotonic (eg PEG-E) or hypertonic (eg NaP or magnesium citrate). The latter agents act by an osmotic effect inducing fluid movement paracellular towards the bowel lumen(e.g. NaP), whereas the former exert their effect by retaining fluid within the bowel lumen (e.g. PEG). Additionally, stimulant laxatives such as sodium picosulphate and bisacodyl are often used in adjunction with osmotic acting agents, to increase the efficacy (2,17). Currently, the preferred method of bowel preparation in the United States, Canada and Europe are PEG-E based solutions in patients with multiple co-morbidities or the extremes of ages. The success of low volume hypertonic NaP solutions has declined especially in patients with co-morbidities due to safety issues. In fact, recent guidelines and an FDA warning advise against the use of NaP, also in healthy individuals because of the risk of phosphate nephropathy (5). Sodium picosulfate/magnesium citrate (P/MC) can be used as an alternative low volume bowel preparation (6,7). Table 1 illustrates the current available colon cleansing regimens in Belgium.

Efficacy and tolerability of current colon cleansing agents

1) polyethylene glycol-electrolyte based solutions

Polyethylene glycol is a macrogol non-absorbable polymer administrated in a electrolyte solution to create a isotonic solution when added to water. The method of action is to introduce an osmotic active agent within the bowel to retain water in the bowel lumen. PEG-E does not induce significant electrolyte or fluid shifts paracellularly because they are osmotically balanced. The downside is that the patient needs to drink large volumes in comparison to hypertonic agents. Traditionally PEG-E solution were given as four liter solution (2,6,7). Numerous trials demonstrate efficacy of these four liter solutions in bowel preparation. The four liter PEG-E solutions are more effective than the historically used diet methods combined with cathertics or high volume balanced solutions or mannitol solutions. Patient's tolerability and palatability is however a major drawback for these agents. Between 5 to 15% of patients in large series do not complete the bowel preparation because of poor taste or a too large volume (18,19). An ample evidence suggest that the main reason of avoiding colonoscopy is intolerability towards a large volume bowel preparation (20). To overcome these intolerabilities numerous changes have been made to the classic PEG-E four liter solution.

Split dose PEG-E solutions

A first strategy to increase the tolerability of four liter PEG-E solutions is to split the solution into two liter solutions administered the night before and the morning of the colonoscopy (21,22). Splitting the total dose of PEG-E into two separated doses results in improved efficacy of bowel cleansing, as suggested by two recent meta-analysis (23,24). Both meta-analysis included mostly high quality randomized trials as illustrated by the Jadad score (23,24). Both meta-analysis clearly document that splitting the dose into two separated doses results in improved bowel cleansing. In addition, the study of Kilgore et al shows a higher tolerability, documented as less nausea, decreased discontinuation and an increased willingness to repeat the same regimen (24). The meta-analysis by Enestvedt *et al*. does not confirm this increased patient tolerability but significant heterogeneity due to difference in protocol and secondary endpoint analysis was present (23). Because of the consistency of these two high quality meta-analysis, recent ESGE guidelines advise a split dose regimen of the PEG-E solution as the preferred method for colon cleansing (5). With the increasing popularity of split dosing, studies also have tried to evaluate the optimal timing between the last bowel cleansing agent dose and colonoscopy.

Table 1. — **Available bowel preparation solutions in Belgium**

ISOTONIC AGENTS		HYPERTONIC AGENTS	
Pure isotonic	**Combination with another laxative**	**Pure hypertonic agents**	**Combination of Hypertonic agents and laxatives**
*PEG-E solutions with high sulfate content : – *Colofort* – *Endopeg* – *Klean-prep* *PEG-E solution with low sulfate content : – *Endofalk* – *Precosol*	*PEG-E and ascorbic acid : – *Moviprep*	*Pure NaP : – *Fleet Phospho Soda*	*Combination of NaP with Biscodyl : – *Prepacol* *Combination of Magnesiumoxide with Picosulfate : – *Picoprep*

Words in bold indicate the general class of the agent. Words in cursive are brands of commercially available agents in Belgium. Abbreviations : PEG : polyethylene glycol solution balanced with electrolytes. NaP : Sodium Phosphate.

This time interval is referred to as the "runway time". Analysis indicate that a short runway time (less than 4 hours) is associated with optimal bowel preparation (5).

Adding additional laxatives

Adding an additional laxative is another strategy to reduce the volume of the PEG-E bowel preparation. Two commonly used laxatives are bisacodyl and ascorbic acid. The aim is to reduce the total volume while maintaining efficacy and increasing tolerability. Bisacodyl is a diphenylmethane compound that is poorly absorbed by the small intestine and stimulates colonic peristalsis. Several trials indicate that adding bisacodyl to a low volume two liter PEG-E solution results in similar bowel cleansing but increased tolerability (17,25-27). Ascorbic acid is absorbed in the small intestine by saturable transport. A dose of ascorbic acid exceeding 1 gram cause full saturation of the transporters, resulting in increased colonic ascorbic acid content where it exerts an osmotic effect (6). The taste resembles oranges and is likely to increase palatability of the solution. Two trials indicate that low volume two liter PEG-E solutions combined with ascorbic acid are equally effective as standard four liter PEG-E, but confer a increased tolerability. These two liter PEG-E solutions with ascorbic acid remain efficient when splitting the dose into an evening and morning dose, making volume related side effects such as nausea less common (28,29). Two trials evaluate bisacodyl versus ascorbic acid as add on to a PEG-E based regimen. The results are however conflicting hereby justifying the usage of either compound, however bisacodyl is often associated with colicky abdominal pain (30,31).

Low sulfate content PEG-E

Sodium sulfates are one of the most abundantly used electrolytes to balance PEG-E solutions. The major drawback of sulphates is the bad taste resembling rotten eggs. Therefore low sulfate PEG-E solutions have been designed in which chloride is the most abundant anion. These solutions confer similar efficacy but have increased palatability, making them better tolerated by patients (7).

2) Sodium phosphate

Sodium phosphate preparations (NaP) are low volume (45 ml) hypertonic solutions that contain monobasic and dibasic sodium phosphate compounds (9). NaP induces significant water shift paracellularly, with a maximal effect 4,6 hours after administration (32). NaP preparations emerged in the late 1980s as an attractive alternative to PEG-E solutions because of its low volume. Safety issues have diminished the widespread success of NaP preparations (see next section). Numerous trials have evaluated the efficacy, tolerability and safety of NaP solutions as compared to four liter PEG-E. These trials differ considerably in dose of PEG-E or NaP and timing of administration of the dose in relation with timing of colonoscopy. As a result of this heterogeneity within randomized controlled trials, several meta-analysis have been conducted (33-35). Tan *et al*. (35) and Juluri *et al*. (34) illustrated in contrast to Belsey (33), that NaP resulted in a better colon preparation and was associated with increased patient tolerability. Still it is important to bear in mind that studies included in the meta-analysis differ in dosing, timing of administration and methodology. Due to the inconsistency between these meta-analysis it seems impossible to draw any conclusions as to whether either preparations is superior to the other with regard to efficacy. More robust meta-analyses comparing four liter PEG-E to NaP are unlikely to resolve this problem because in clinical practice four liter PEG-E solutions are mostly replaced by low volume PEG-E solutions combined with laxatives. Also, safety issues regarding NaP resulted in guidelines advising against its routine use and the option of new and safer hypertonic colon solutions such as magnesiumoxide (combined with picosulfate) will result in possible further decline of the use of NaP (12,36). An additional problem of NaP is its ability to induce mucosal lesions , resembling apthoid erosions. This may compromise mucosal interpretation, especially in patients with inflammatory bowel disease (37). Despite safety issues, NaP is still regarded as an efficient colon cleanser, resulting in geographical differences in popularity (12).

3) sodium picosulfate/ Magnesium citrate

Magnesium is administered in a magnesium oxide form together with citrate. Within the bowel lumen magnesium loses its bond with the oxide anion forming a magnesium citrate compound. Magnesium citrate is a hypertonic laxative that causes osmotic shift and increases intestinal transit. Magnesium itself additionally stimulates intestinal transit through the release of cholecystokinin. Picosulfate is metabolized in the bowel by bacteria to its active metabolite generating enhanced colonic transit and inhibiting colonic uptake of electrolytes and fluids. Several trials documented the excellent efficacy and tolerability of sodium picosulfate combined with magnesium citrate (P/MC) as compared to PEG-E and NaP (38-44). These trials document non-inferiority or even superiority of P/MC as compared to PEG-E and NaP with regard to efficacy and patient tolerability. P/MC has been cleared for colonoscopy preparation by the European Medicine Agency in 2010 and by the FDA in 2012 (38,42).

Safety issues regarding colon cleansing agents

1) General safety issues

In addition to efficacy and patient tolerability, safety is a major determinant when choosing the right bowel preparation. In general, according to published studies, all bowel cleaning agents are safe in healthy individuals

Table 2. — **General Contra-indications for bowel preparation**

– Paralytic ileus
– Mechanical bowel obstruction
– Hemodynamic instability
-– Bowel perforation
-– inability to protect airway
-– gastric outlet syndrome

without significant co-morbidity (7). Certain conditions are however contra-indications for bowel preparation irrespective of the bowel cleaning agent used. Table 2 highlights general contra-indications for bowel preparation. Because all current bowel cleaning agents exert an osmotic effect, chances in fluid and electrolytes are possible. Still the ability to induce significant hemodynamic changes or electrolyte changes are more important in the group of hypertonic bowel preparation agents (NaP, P/MC) as compared to the group of isotonic agents (PEG-E) (15). The ability to induce fluid and electrolyte changes is especially important in elderly patients and/or patients with renal disease, cardiac disease (especially when on ACE-inhibitors) or hepatic disease. In general, but certainly in patients with these co-morbidities, adequate hydration during bowel preparation is crucial (14). Due to the increased sensitivity for fluid and electrolyte imbalances in the elderly and patients with cardiac, renal and hepatic co-morbidities, PEG-E solutions are the preferred method of bowel preparation in these populations (14,15).

2) Compound specific safety issues

Table 3 highlights more severe compound specific safety issues. Clinical trials often report mild side effects such as nausea, vomiting, abdominal cramping and headache. Severe side effects such as highlighted in table 3 are fortunately rare. Severe side-effects are mostly reported outside clinical trials in case reports and retrospective case series. This underscores the importance of post-marketing surveillance, when bowel preparations are being used in clinical practice in patients with more co-morbidities, often excluded in clinical trials.

polyethylene glycol-electrolyte based solutions

PEG-E solution are in generally the safest bowel cleaning agents, especially in patients with cardiac, renal or hepatic co-morbidities sensitizing patients to fluid and electrolyte imbalances. However, severe side effects have been reported after PEG-E use (15). Side effects relate to the ingestion of rather large volumes of PEG such as vomiting with development of esophagus rupture, Mallory-Weiss tears or aspiration have been reported (46-49). Reports of allergic reaction to PEG-E and pancreatitis also exist (50,51). Although iso-osmotically balanced, PEG-E still has the rare ability to induce hypovolemia combined with dysnatremia due to diarrhea, vomiting and inadequate hydration during preparation. Hyponatremic hypovolemia can occur when PEG-E induced volume loss results in an up regulation of arginine vasopressine, retaining more free water than sodium (52). When patients are unable to compensate for intestinal losses (such as the elderly with diminished thirst sensation) hypernatremic hypovolemia can occur (15). Although dysnatremia can occur after the use of PEG-E preparations, it is rarely clinically relevant.

Sodium phosphate

Due to its hypertonic nature, NaP has a more potent effect of inducing alterations in fluid and electrolyte homeostasis. These homeostatic alterations result in clinically relevant side effects in patients with co-morbidities, making NaP contra-indicated as a bowel cleanser in patients with electrolyte disturbances, cirrhosis, chronic kidney disease, congestive heart failure or recent myocardial infarction (7). Another alarming and unique feature of NaP is related to the phosphorus anion ability to induce hyperphosphatemia. Hyperphosphatemia occurs in up to 40% of healthy patients (53). In a retrospective analysis of 9799 patients undergoing colonoscopy, NaP solutions are associated in a multiple logistic regression model with an increased risk of acute kidney injury (54). Acute phosphate nephropathy (APN) is the term coined to acute renal failure associated with NaP solution. In APN, supraphysiologic levels of phosphorus precipitate within the renal tubuli as calcium phosphate crystals. Risk factors associated with APN are female sex, low body weight, old age (> 65 year old), chronic kidney disease, hypertension, diabetes mellitus, congestive heart failure and treatment with medications affecting the renal clearance (ACE-inhibitors, angiotens receptor blokkers and diuretics). As a result of numerous reported cases of APN (55-66), the FDA issued a black

Table 3. — **Compound specific safety issues**

polyethylene glycol-electrolyte based solutions	Sodium phosphate	sodium picosulfate combined with magnesium citrate
Hyponatremia Hypernatremia Hypokalemia Aspiration Mallory Weiss Tears Allergic reaction Pancreatitis	Hyponatremia Hypernatremia Hyperphosphatemie Hypocalcemia Acute phosphate nephropathy Mucosa alterations (aphthous lesions)	Hyponatremie Hypermagnesemia Dehydration

box warning against NaP in 2008, stating its use should be avoided in patients older than 55 years old, younger than 18 year and patients suffering from renal, cardiac or liver disease or taking medications such as ACE-inhibitors, angiotens receptor blokkers or diuretics (67). The recent published ESGE-guidelines advise against routine use of NaP. These guidelines do suggest that NaP is a therapeutic option for patients in which other bowel preparing agents are insufficient (for example volume related side-effects of PEG-E), although careful monitoring of renal function is advised.

Sodium picosulfate/magnesium citrate

Although P/MC solutions are the most recent approved bowel cleansing by large drug authority agencies, clinical experience is rather extensive with over 28 million exposures last four decades (38). Because the magnesium citrate compound of P/MC is a hypertonic agent, it has the ability to induce more profound fluid shifts than PEG-E. A recent study illustrates the ability of P/MC to induce significant dehydration, necessitating an average of two liter intravenous fluid compensation (68). Cases of syncope secondary to P/MC induced hypovolemia have been reported (69). Rare cases of hyponatremia have also been reported (70,71), but concomitant thiazide use contributed to the hyponatremia in at least one case (70). Finally, a transient rise in magnesium levels has also been reported, especially in elderly patient (72). The latter are probably more prone to transient rises in magnesium because of an age related decline in GFR, with renal excretion being the predominant regulated mechanism of magnesium excretion. Still clinically relevant cases of hypermagnesemia secondary to P/MC a rare (73,74).

3) Safety measures

Regardless of the type bowel preparation used (PEG-E, NaP or P/MC), fluid and electrolyte imbalances can occur, underscoring the importance of adequate hydration during bowel preparation (14). Because isotonic agents such as PEG-E induce less profound fluid shifts, they are regarded as the preferred option in patients prone to fluid and electrolyte imbalances (15). Proper patients selection with regards to age, co-morbidities and baseline electrolyte panel should allow for a safe and individualized bowel preparation selection.

Conclusion

Colonoscopy is the most frequently used diagnostic technique to evaluate the colonic mucosa. Mucosal visualization and hence the diagnostic performance of colonoscopy largely depends upon the degree of bowel preparation. To date not a single best bowel cleansing agent has been identified. Patient and physician based preferences may somewhat differ in respect to efficacy, tolerability and safety, with physician weighing efficacy and patients weighing tolerability as a major determent of bowel preparation. Post marketing surveillance has raised safety issues regarding the use of NaP, making safety a major determent for the choice of bowel cleaning agents in daily clinical practice. PEG-E solutions are considered the safer choice in patients prone to fluid and electrolyte imbalances as compared to the hypertonic alternatives (NaP of P/MC). The inability of PEG-E to alter the mucosal morphology is also an important characteristic in patients with inflammatory bowel disease. For the healthy individual numerous bowel cleaning agents exist. Hypertonic agents have an outstanding tolerability due to their low volume as compared to PEG-E. Still changes to the PEG-E regimen (adding laxatives such as bisacodyl or ascorbic acid or split dosing) resulted in increased tolerability. These strategies of split dosing or adding another laxative should be applied when choosing a PEG-E regimen. Choosing a low volume hypertonic agent for otherwise healthy individuals seems a perfect reasonable choice. Due to safety issues NaP, is no longer advised by recent ESGE guidelines, explaining the increasing popularity of the low volume hypertonic alternative P/MC. Further innovation in the field of bowel cleaning agents will hopefully help to identify a universal preferred agent.

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