

## Addition of Simethicone to Polyethylene Glycol Electrolyte Solution for Bowel Preparation Improves Colonoscopic Bowel Visualization: A Review

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### Abstract

Colorectal cancer, usually diagnosed more in the developed countries (western), is a cancer whose morbidity and mortality rate can be significantly reduced by screening early and removing the pre-malignant adenomas. The only effective way to properly visualize the entire colon is via colonoscopy. For optimum high quality colonoscopy, effective bowel preparation is an absolute requirement, as an incomplete colonoscopy can reduce the likelihood of detecting adenomas or polyps. It can also increase the duration of the procedure, negatively influence the patient's tolerability and the performing doctor's satisfaction. Additionally, it can cause a higher risk of complications. The most common limitation a physician can encounter during a routine colonoscopy coalesce with bile and gastric contents. Additionally, the presence of air bubbles can affect the proper visualization of the entire colon. Prior to a colonoscopy, physicians routinely use a variety of laxatives for bowel preparation. Although there is no guarantee for optimal safety and efficacy, all of them have unique positive and negative qualities. In this review, we will evaluate the effect of Simethicone when it is combined with polyethylene glycol whereby the amount of colonic bubbles and duration of a colonoscopy procedure is reduced.

**Keywords:** Colonoscopy, simethicone, polyethylene glycol, bowel preparation.

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### Introduction

Colorectal cancer (CRC) is one of the most diagnosed cancers in Europe and the second leading cause of death from cancer diseases in Europe [1]. In the United States CRC is also one of the leading causes of morbidity and mortality, exceeding more than 148,000 new cases and 49,000 cancer related deaths in past five years, five-year survival rate is approximately 90% if the disease is discovered earlier (i.e. T1 within the submucosal layer, or T2 within the mucosal layer), 68% if the disease spread regionally (i.e. any T, N1-3, MO), while those with distant metastases (any T, any N, M1) have 5-10% of five-year survival rate [1,2]. Early detection can prevent CRC and the removal of adenomas or localized cancer, for patients with symptoms and other positive CRC screening tests. Colonoscopy is generally accepted as the gold standard for diagnostic evaluation, and therapeutic maneuvers for lower gastrointestinal disorders. Abdominal pain, gastrointestinal bleeding, unusual bowel habits and anemia are the most common indications for the performing a colonoscopy. Level of bowel preparation needed to be, a colon without residual stool, brown liquid, or bubbles over the mucosa are all necessary for a successful colonoscopy [4].

This review we will not only assess the effect of Simethicone when it is combined with polyethylene

glycol whereby the amount of colonic bubbles and duration of a colonoscopy procedure is reduced, but also evaluate different clinical conditions and the effects it has on these conditions.

### 1. Factors associated with poor bowel preparation

According to recent studies done in the United Kingdom, 1 in 5 incomplete colonoscopies occur due to poor bowel preparation that prevents the completion of the procedure [5]. Inadequate bowel preparation is linked with the reduced detection rates of adenoma, extended operation time, inability to reach cecum intubation and mucosal visualization efficiently, it also reduces patient's tolerability and doctor's contentment toward the procedure, and a higher risk of complications [6]. A prospective study from 11 European countries studied 5832 patients in 21 centers examined the link of preparation quality and polyp identification during colonoscopy carried out for a range of common indications a good quality groundwork is linked with identification of polyps of all sizes (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.28–2.36), and with polyps bigger than 10 mm in size (OR, 1.72; 95% CI, 1.11–2.67) [7]. Prolonged use of psychotropic drugs, constipation, incomplete intake of preparation aperients are some of the factors associated with poor bowel preparation whereas patients awareness to avoid vegetables prior

to the procedure as well as completion of cleansing agent are related with a suitable bowel preparation quality. Some of other risk factors for incomplete colonoscopy include inadequate bowel cleansing, prior history of pelvic or abdominal surgery and female gender [8-10]. Other studies have concluded that independent predictors of an insufficient bowel preparation include history of colorectal resection, appendectomy, hysterectomy, diabetes and age exceeding 60 years [11].

The presence of colonic bubbles, foam, and mucus gathered in the gastrointestinal tract is a significant factor that can influence mucosal visualization diminishing the quality of colonoscopy and could cause the procedure to be delayed as well as give rise to probable risk of missing subtle lesions [12,13]. Sidhu et al evaluated all of colonoscopies performed from April 2005 to 2010 at the Royal Liverpool University the study found 8910 colonoscopies performed, 693 were unfinished (7.8%; 58% women; mean age, 61 years), and insufficient bowel preparation was the most shared reason for incomplete colonoscopy, accounting for almost 25% of failed colonoscopies in their consequence [14]. A suitable preparation for colonoscopy should be able to eliminate the bubbles, causes no histological or physiological modification, not having side effects or changes in fluids or electrolytes, can be tolerable for patients, and be suitable for most patients in different conditions [15]. Presently a number of purgatives are used in clinical practice for bowel preparation preceding to colonoscopy [16]. While none has delivered optimal safety and efficacy profiles, each signifies unique strengths and weaknesses [17].

## **2. Polyethylene glycol (PEG)**

PEG electrolyte solution (PEG-ELS) was introduced by Davis *et al.* in early 1980s and it consists of an isotonic oral, and non-digestible lavage, i.e. it passes through the bowel without intestinal absorption or secretion [18]. PEG-ELS does not result in any main physiological changes nor histologic features of the colonic mucosa and can be used in patients suspected of inflammatory bowel disease without concealing the diagnostic capabilities of colonoscopy or tissue sample analysis [19]. It considered to be safe for patients with pre-existing electrolyte imbalances and for patients who have complication (e.g. those with kidney failure, advanced heart disease, or liver disease with ascites), its contraindicated to patients with perforation, gastrointestinal obstruction, severe inflammatory bowel disease (IBD), ileus or gastric retention [20]. American society of Colon and rectal

surgeons, the American Society for Gastrointestinal Endoscopic (ASGE), the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) suggested PEG as a gold standard bowel preparation regimen for colonoscopy [21].

### **2.1 Split or single doses and adverse events**

Due to its large volume of fluid ingesting and salty taste is highly implantable and mentioned by patients as a key cause for not finishing the dosing regimen; the resultant insufficient bowel preparation has led to these patients recurrently demanding repeat colonoscopy, with the range of unremoved fecal obstruction sometimes completely preventing visualization [22]. Preparations are achieved by using 4-L split-dose PEG-ELS regimens, and this is considered to be the present criterion standard colonoscopy preparation, in which the first half dosage is ingested on the day before and the second half dosage is ingested early morning of the day of procedure which have been shown to be more effective for colon laxative than single dosage administration on the day before [23]. When dosage is divided on a routinely 4-liter PEG volume was established to be as effective as, and better accepted than, the bolus dose given 1 day prior to the procedure [24].

Active control, single-blind, prospective, randomized study conducted in Italy assessed the extent of colon purgative, comparing with a split-dosage versus full dosage. The split-dosage regimen exhibited a remarkably increased degree of colon cleansing in all colon segments, whilst the difference was greatest in proximal colon sections. The split-dosage intake schedule most probably improves cecum intubation and polyp detection rates [25].

In 2013 European Society of Gastrointestinal Endoscopy (ESGE) highly recommended a divided regimen of 4 L PEG solution (or a same day regimen in the event of afternoon colonoscopy) for repetitive bowel preparation, according to their report a divided dose regimen of PEG considerably improved the percentage of patients with satisfactory colon cleanliness, significantly increased patient compliance, and considerably decreased nausea [26]. US Multi-Society Task Force on Colorectal Cancer also strongly recommended the use of a divided dose for bowel cleansing shows higher efficacy with a divided dose matched with the traditional regimen of administering the preparation the day prior to the procedure [27].

In patients with a lower gastrointestinal hemorrhage, usage of high-dose (6-8 L) PEG-ELS lavage via a

nasal gastric tube is effective as a form of rapid bowel preparation(1). Exacerbation of inappropriate antidiuretic hormone secretion syndrome, Mallory-Weiss tear, nausea with and without vomiting, rare pulmonary aspiration, abdominal pain, cardiac arrhythmia, lavage-induced pill malabsorption, pancreatitis as well as colitis have been reported as adverse effects in patients taking PEG-ELS [29-31].

### 3. Simethicone

Simethicone, a solvent that is made up of a chemical combination of dimethyl polysiloxane and silica gel, is nontoxic and physiologically inactive, it has the option to be ingested orally and is unable to be absorbed through the gastrointestinal system [32]. It has been shown to rarely have side effects. It is a defoaming agent that lowers surface tension which in turn leads to coalescing of bubbles and foam, it additionally uses as a supplement treatment for patients with gastrointestinal distension that caused by gas. When PEG-ELS is combined together with simethicone, it substantially eliminates the mucosal foam and bubbles by reducing surface tension, gas, and bloating, flushing is also reduced during the procedure, in 2013 The ESGE proposes adding simethicone to standard bowel preparation [33-35]. A prospective, randomized, investigator-blinded study from USA comparing 2 liters PEG-ELS to PEG-ELS with simethicone (PEG-S) investigate 123 patients 62 had taken PEG-S and 61 PEG-ELS. The incidence of grade B or C bubbles (bubble assessment scale: **A**: no/minimal bubbles, **B**: moderate bubbles, **C**: severe bubbles "Figure 1") was much inferior with PEG-S matched with PEG-ELS (2% vs. 38%;  $P=0.001$ ); More PEG-S patients had tremendous rather than good preps (whole colon 53% vs. 28%,  $P=0.004$ ; right colon 53% vs. 35%,  $P=0.044$ ), concurrent with previous studies these studies found an increased occurrence of bubbles with the control aperient, and a remarked reduction of bubbles with the addition of simethicone [6,36]. In a prospective study 26 patients received simethicone ( $n = 14$ ) or placebo to evaluate whether simethicone played a part in improving visibility when administered the night before colonoscopy, quantity of bubbles and extent of vagueness were analyzed as the two parameters of visibility, patients who had simethicone had comparatively less bubbles ( $p$  less than 0.02), though vagueness was not improved ( $p = 0.9$ ), a soiled detritus that interfered with the colonoscopic examination was observed similarly in both groups [37].

Several studies report that adding of simethicone to PEG-ELS preceding to colonoscopy for bowel preparation enhances the clearance of excessive gas in the gastrointestinal tract(GIT) and decreases bloating, abdominal discomfort, and abdominal pain and increases visualization in the GIT [38,39].



**Figure 1:** Grade of air bubbles: A: no and slight air bubbles (no bubbles and  $\leq 25\%$  bubbles), B: moderate air bubbles (25%~50% bubbles), C: severe air bubbles ( $\geq 50\%$  bubbles).

#### 3.1 Patient's tolerability, adverse events and procedure timing

A prospective, double-blind, placebo, controlled study assesses the effectiveness of simethicone in augmenting visibility and efficacy during colonoscopy matching with PEG-ELS alone. Using a different grading scale that included the esophagus and duodenum concluded that 133.3mg (2 mL) of liquid Simethicone dissolved in 60mL water for about 25 minutes before the procedure could enhance the visibility as well as minimizing the number of flushing needed to remove the mucus significantly. The study goes further to demonstrate that using Simethicone before endoscopy would reduce the duration of the procedure thus leading to more satisfaction to the patient as well as the physician [33](2). Tongprasert S et al conducted a study with 124 patients receiving 2 doses of sodium phosphate together with 240mg of tablet simethicone or placebo as colon preparation to contrast total colonoscopic time, side effects of medication as well as physician

and patient satisfaction. The study found that, endoscopist and patient satisfaction was relatively higher in simethicone group than that in the placebo group (79.0% vs 32.8%,  $P < 0.0001$  and  $8.7 \pm 1.8$  vs  $7.6 \pm 1.9$ ,  $P = 0.002$ ), the improvement in patient satisfaction may be attributed to reduction in gas and abdominal discomfort by simethicone during the procedure. This could thus encourage patient to undertake repeated colonoscopies in the future. However no significant difference in duration of colonoscopy was noted in the two groups. ( $25.1 \pm 13.1$  vs  $27.3 \pm 12.9$  min,  $P = 0.27$ ) [40]. Lazzaroni et al reported remarkably reduced malaise and sleep disturbances as well as enhanced tolerance when simethicone was used in together with PEG-ELS [41].

Overall, simethicone does not substantially change the quality of the bowel preparation; however, it does cut the number of adherent bubbles present, which may boost colonic visualization.

#### **4. Special patient subpopulation**

##### **4.1 Elderly patients**

Patients who are advanced in age have a higher percentage change of having poor bowel preparations. This is mainly due to higher incidence of severe constipation and slower colonic transit [42]. Meta-analysis and a systematic review of 20 studies have reported poor bowel preparation in 18.8% of patients above 65 years and 12.1% in patients over 80 years. The study also shed light on the likelihood that elderly patients have a much higher statistical chance to have adverse effects after colonoscopy. GI adverse events such as perforation and bleeding as well as cardiovascular and pulmonary complications are shown to be the most common complications [43]. The colonoscopy completion rates in older patients have been proven to be a domino effect of inadequate bowel preparation [44]. 4 L of polyethylene ethylene glycol, the most frequently used bowel preparation purgative, required for a large ingestion volume for elderly patients, these patients have a statistically higher chance of having, cardiopulmonary, hepatic or renal conditions. Due to this, they are ineligible to consume large amount of such fluids, there have been small volume of alternative osmotic laxatives such as sodium Pico sulfate or sodium sulfate. Also, repeated trips to the commode results an increased risk for the fragile elderly patient with mobility issues [45]. Owing to its substantial volume, PEG is contraindicated for patients who have abnormal swallowing function, stroke, dementia, and

Parkinson's disease. All of which are more often associated with the elderly [46].

##### **4.2 Diabetic patients**

PEG-based colon cleansing solutions are often accepted as safe to be administered to patients with electrolyte imbalances. Often though, patients with diabetes have reduced renal perfusion even though the serum creatinine is normal [47]. Several studies have advised to closely monitor the patient's electrolyte after colonoscopy, especially patients with renal or cardiac failure, as patients with diabetes have significantly subpar preparations with PEG solutions as compared to the non-diabetics according [45,48].

##### **4.3 Pediatric population**

Even though there is no nationwide standard for pediatric bowel preparations for colonoscopy, clinical studies have been conducted to evaluate the use of PEG for pediatric bowel preparation regimens. Advices PEG-ELS as an effective preparation regimen but an inpatient admission is more often than not required for nasogastric tube administration otherwise the volume is limited by taste [49-51]. Simethicone has been marketed off-exchange trading for more than 5 decades, and is considered quite safe across all age groups. ASGE 2014 have a recommended guideline that requires an administration of polyethylene glycol with electrolytes through a nasogastric tube, this should be done in a hospital environment for 24 hours before the procedure and is a safe and accepted regimen, especially in children younger than 6 years of age [36].

##### **4.4 Patients with renal failure**

PEG is the only recommended bowel preparation as per ESGE's recommendation for patients presenting with renal failure. The wait between the last dose of colon preparation and colonoscopy should be minimal and less than 4 hours [52,53]. The schedule of dialysis should be regulated according to the intravascular volume status owing to the fact that PEG may augmenting the intravascular volume. to sustain the residual renal function patients with peritoneal dialysis should avoid intravascular volume depletion. Evaluate kidney function prior to and after the procedure. Medications that may have an association with kidney function (e.g. ACEI, ARB and diuretics) should be discontinued on the day of receiving of oral bowel preparation agents and until 3 days post the colonoscopy [54, 55].

#### 4.5 Pregnancy

During pregnancy, colonoscopy is rarely advised. If there is an absolute necessity it should be put on hold until the second trimester whenever possible, a careful assessment of risk vs benefit is needed as well as a strong indication for the procedure [56, 57]. According to US food and drug administration (FDA) both PEG-ELS solutions and simethicone are classified as category C medications [58]. However a study of 225 pregnant women on treatment for constipation showed that low doses of PEG-ELS were considered to be safe [59]. American Gastroenterological Association recommends tap water enemas rather than PEG-ELS, though it's a low risk option, for lower endoscopy considering that full endoscopy is rarely indicated during pregnancy [60]

#### Conclusion

Addition of simethicone to PEG-ELS efficiently removes bubbles, significantly reduces the need for flushing, and results in more tremendous preparations, This provides the likelihood of more accurate assessment of the mucosa , without encountering any side effects, physician and patient satisfaction is also increased , in generally speaking a split dose of 2 liters PEG each starting on the evening of the day before and the day of procedure is recommended ,as PEG-based bowel preparation is suitable in most situations in terms of safety considerations ,but special consideration of the patients, including elderly patients and patients with comorbidity , should be evaluated in order to provide them with harmless and more effective method of bowel preparation.

#### Conflict of Interest

The author has no actual or potential conflicts of interest to declare.

#### Abbreviations

**CRC:** colorectal cancer

**PEG:** polyethylene glycol

**PEG-ELS:** Polyethylene glycol electrolyte solution

**IBD:** inflammatory bowel disease

**ASGE:** American society for gastrointestinal endoscopic

**SAGES:** society of American gastrointestinal and endoscopic surgeons

**ESGE:** European Society of Gastrointestinal Endoscopy

**GIT:** gastrointestinal tract

**ACEI:** angiotensin-converting-enzyme inhibitor

**ARB:** Angiotensin receptor blockers

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