

Commonly used preparations for colonoscopy: Efficacy, tolerability and safety – A Canadian Association of Gastroenterology position paper

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INTRODUCTION: The increased demand for colonoscopy, coupled with the introduction of new bowel cleansing preparations and recent caution advisories in Canada, has prompted a review of bowel preparations by the Canadian Association of Gastroenterology.

METHODS: The present review was conducted by the Clinical Affairs group of committees including the endoscopy, hepatobiliary/transplant, liaison, pediatrics, practice affairs and regional representation committees, along with the assistance of Canadian experts in the field. An effort was made to systematically assess randomized prospective trials evaluating commonly used bowel cleansing preparations in Canada.

RESULTS: Polyethylene glycol (PEG)-; sodium phosphate (NaP)-; magnesium citrate (Mg-citrate)-; and sodium picosulfate, citric acid and magnesium oxide (PSMC)-containing preparations were reviewed. Regimens of PEG 2 L with bisacodyl (10 mg to 20 mg) or Mg-citrate (296 mL) are as effective as standard PEG 4 L regimens, but are better tolerated. NaP preparations appear more effective and better tolerated than standard PEG solutions. PSMC has good efficacy and tolerability but head-to-head trials with NaP solutions remain few, and conclusions equivocal. Adequate hydration during preparation and up to the time of colonoscopy is critical in minimizing side effects and improving bowel cleansing in patients receiving NaP and PSMC preparations. All preparations may cause adverse events, including rare, serious outcomes. NaP should not be used in patients with cardiac or renal dysfunction (PEG solution is preferable in these patients), bowel obstruction or ascites, and caution should be exercised when used in patients with pre-existing electrolyte disturbances, those taking medications that may affect electrolyte levels and elderly or debilitated patients. Health Canada's recommended NaP dosing for most patients is two 45 mL doses 24 h apart. However, both safety and efficacy data on this dosing schedule are lacking. Many members of the Canadian Association of Gastroenterology expert panel administer both doses within 24 h, as studied in clinical trials, after careful one-on-one discussion of risks and benefits in carefully selected patients. Safety data on PSMC and combination preparations in North America are limited and clinicians are encouraged to keep abreast of developments in this area.

CONCLUSIONS: All four preparations reviewed provided effective bowel cleansing for colonoscopy in the majority of patients, with varying tolerability. Adequate hydration is essential in patients receiving the preparations.

Key Words: Colon preparation; Colonoscopy; Polyethylene glycol; Sodium phosphate

L'efficacité, la tolérabilité et l'innocuité de préparations de coloscopie courantes : Un document de principes de l'Association canadienne de gastroentérologie

INTRODUCTION : La demande accrue de coloscopies, couplée à l'apparition de nouvelles préparations intestinales et de récentes mises en garde au Canada, a incité l'Association canadienne de gastroentérologie à analyser les préparations intestinales.

MÉTHODOLOGIE : Le groupe des comités des affaires cliniques a procédé à la présente analyse, y compris les comités sur l'endoscopie, les troubles hépatobiliaires et les greffes, les représentants, la pédiatrie, les affaires de pratique et les représentants régionaux, avec l'aide d'experts canadiens dans le domaine. On s'est efforcé d'évaluer systématiquement les essais aléatoires et prospectifs sur les principales préparations intestinales au Canada.

RÉSULTATS : Les préparations contenant du polyéthylène-glycol (PEG), du phosphate de sodium (NaP), ainsi que du citrate de magnésium, du picosulfate sodique, de l'acide citrique et de l'hydroxyde de magnésium (PSMC), ont été analysées. Les posologies de 2 litres de PEG conjuguées à du bisacodyl (10 mg à 20 mg) ou à du citrate de magnésium (296 mL) sont aussi efficaces qu'une posologie standard de 4 litres de PEG, mais mieux tolérées. Les préparations de NaP semblent plus efficaces et mieux tolérées que les solutions de PEG standard. Les préparations de PSMC affichent une bonne efficacité et une bonne tolérabilité, mais les essais par rapport aux solutions de NaP sont rares, et les conclusions sont équivoques. Il est essentiel d'assurer une hydratation suffisante entre la préparation et à la coloscopie pour réduire les effets secondaires au minimum et améliorer la purge intestinale des patients qui reçoivent des préparations de NaP et de PSMC. Toutes les préparations peuvent s'associer à des effets indésirables, y compris des issues rares et graves. Le NaP ne devrait pas être utilisé chez les patients atteints d'un dysfonctionnement cardiaque ou rénal (la solution de PEG est alors préférable), d'occlusion intestinale ou d'asciites, et il faut les utiliser avec prudence chez les patients ayant déjà des troubles électrolytiques, qui prennent des médicaments susceptibles de nuire aux taux d'électrolytes ou qui sont âgés ou atteints de maladies débilitantes. Pour la plupart des patients, Santé Canada recommande d'administrer deux doses de 45 mL à 24 heures d'intervalle. Cependant, il n'existe pas de données d'innocuité et d'efficacité sur un tel mode d'administration. De nombreux membres du comité d'experts de l'Association canadienne de gastroentérologie administrent les deux doses en 24 heures, conformément aux essais cliniques, après avoir procédé à une évaluation attentive des risques et des bienfaits auprès de patients soigneusement sélectionnés. Les données d'innocuité sur le PSMC et les préparations combinées sont limitées en Amérique du Nord, et les cliniciens sont invités à se tenir au courant de l'évolution de ce domaine.

CONCLUSIONS : Les quatre préparations analysées assuraient un nettoyage intestinal efficace pour la coloscopie chez la majorité des patients et s'associaient à une tolérabilité variable. Il est essentiel de fournir une hydratation efficace aux patients qui reçoivent les préparations.

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In Canada, colorectal cancer is the second most common cause of cancer-related death (1). In addition to its use in screening for and managing colorectal cancer, colonoscopy is used to assess gastrointestinal or rectal bleeding, abdominal pain, anemia, irritable or inflammatory bowel symptoms, and other gastrointestinal signs and symptoms (2,3).

Adequate colon preparation is required for successful visualization of the colon, and essential for the detection of suspicious lesions. However, studies using large databases reveal that up to 23% of all colonoscopies have suboptimal bowel preparation (4) resulting in lower cecal intubation rates (5), longer procedural times (6) and decreased polyp detection (4,6). Inadequate preparation may lead to incomplete visualization of the colon, resulting in shortened screening intervals due to concerns about missed lesions (7). This will further increase the demand and waiting times for colonoscopy.

There are many reasons for an inadequate colonic preparation. Poor compliance due to incomplete consumption of the colon preparation is a strong influence (8), with excess bowel preparation volume cited as the most common deterrent to colonoscopy (9). Preparations must be selected based on optimal efficacy and tolerability while also remaining safe.

The increased demand for colonoscopy, attributable to widespread colorectal cancer screening and surveillance, coupled with the introduction of new bowel cleansing preparations and recent caution advisories in Canada, has prompted a review of bowel preparations by the Canadian Association of Gastroenterology (CAG). The present review was conducted by the Clinical Affairs group of committees including the endoscopy, hepatobiliary/transplant, liaison, pediatrics, practice affairs and regional representation committees, along with the assistance of Canadian experts in the field. The reader is also referred to a recent multisociety American publication (10) on the present topic.

OVERVIEW OF BOWEL CLEANSING PREPARATIONS

Adequate bowel cleansing may be achieved through a variety of mechanisms. Recommendations for diet and hydration vary from centre to centre and will not be discussed in the present review. Commonly used bowel cleansing preparations in Canada include polyethylene glycol (PEG)-; sodium phosphate (NaP)-; magnesium citrate (Mg-citrate)-; and sodium picosulphate, citric acid and magnesium oxide (PSMC)-containing preparations.

The mechanism of action of these compounds has an impact on the choice of preparations in patients with comorbidities (see Safety section). PEG-containing preparations (eg, GoLYTELY, Braintree Laboratories Inc, Canada; Colyte, Zymcan Pharmaceuticals Inc, Canada; Peglyte, Pharmascience Inc, Canada and Klean-Prep, Rivex Pharma Inc, Canada) are large-volume, osmotically balanced solutions that act as purgatives to evacuate the intestine through the ingestion of nonabsorbable fluid.

NaP-based preparations (eg, Fleet Phospho-Soda, Johnson & Johnson – Merck Consumer Pharmaceuticals of Canada and Enemol, Dominion Pharmacal, Canada) are small-volume, hyperosmotic solutions that exert their purgative action through osmotically drawing fluid into the intestinal lumen. PSMC (Pico-Salax, Ferring Pharmaceuticals Inc, Canada) contains sodium picosulphate (which decreases water and electrolyte absorption, as well as increases motility) and Mg-citrate (an osmotic laxative).

Mg-citrate (eg, Citro-Mag, Rougier Pharma, Canada) is a hyperosmolar laxative that also exerts its effect by enhancing intestinal peristalsis and stimulating the release of cholecystokinin (11) to cause secretory diarrhea. Historically, Mg-citrate was mainly used in preparations for radiological imaging tests of the colon.

Sample costs for these bowel preparations are shown in Table 1. These costs may vary depending on the location and pharmacy where they are purchased. However, the cost-effectiveness of bowel preparations should reflect the cost of re-examination as a result of inadequate bowel preparation if that is an issue with a particular preparation (7,9).

EFFICACY AND TOLERABILITY

The literature on colon preparations includes studies of varying degrees of quality, with disparate definitions of validated and nonvalidated tools of outcome measurement, and varying patient populations and preparation protocols. The present review includes primarily randomized controlled trials (RCTs) that assess the efficacy and tolerability of the four types of preparations in patients undergoing colonoscopy. Studies assessing bowel preparations for barium enema were not included because the efficacy implications may be quite different. Many of the trials compare two or more bowel preparations; therefore, some repetition in the sections for the different preparations was necessary to allow easy access to information.

PEG

PEG has been available since 1980 and its efficacy was established compared with older diet and cathartic regimens (12,13). Sixteen trials (14-29) compared PEG with NaP (Table 2). NaP was superior to PEG in efficacy in six of 16 trials, and was superior in tolerability and acceptability in seven of 16 trials. Only two trials (29,30) suggested that PEG was superior to NaP with regards to efficacy. Even after bisacodyl was added to PEG, NaP continued to be more effective and better tolerated (31). In general, more patients receiving NaP than PEG were willing to repeat the preparation (17-19,32), while those who had previously used PEG expressed a preference for using NaP in the future (14,22).

In separate trials, PEG was no more effective than bisacodyl or senna, with no differences in tolerability and acceptability (Table 3) (33,34).

More studies (33-46) have focused on ways to increase the efficacy and patient tolerability and acceptability of PEG (Table 3). The addition of bisacodyl, senna or Mg-citrate to PEG increased the efficacy compared with PEG alone, without decreasing tolerability and acceptability (35-37). Although PEG is generally well tolerated, 5% to 38% of patients do not complete the preparation because of poor palatability or large volume (16,18,38). Use of low-volume PEG 2 L in combination with Mg-citrate (39), bisacodyl (39-42) or senna (38) was generally better tolerated than PEG 4 L, but efficacy varied (Table 3). PEG 2 L plus bisacodyl (10 mg to 20 mg) or Mg-citrate (296 mL) was at least as effective as PEG 4 L (39-42), but PEG 2 L plus senna was not (38). Use of PEG 1.5 L or 2 L with PSMC was equally or less effective than PEG 4 L, but with no improvement in tolerability and acceptability (43,44). Two studies (45,46) found that administering PEG 4 L or 3 L (with or without bisacodyl) in divided doses, reduced the need for dietary restrictions, improved efficacy, and in one study (46) improved tolerability and acceptability. Despite these limitations, PEG is

COPYRIGHT PULSUS GROUP INC. - DO NOT COPY**TABLE 1**
Relative cost of bowel cleansing preparations

Preparation	Product	Hospital cost	Retail cost	Suggested retail price
Magnesium citrate	Citro-Mag* (300 mL)	\$1.55	\$2.44	\$4.79
Sodium phosphate	Fleet Phospho-Soda† (45 mL)	\$2.69 × 2 = \$5.38	\$3.77 × 2 = \$7.54	\$6.99 × 2 = \$13.98
Polyethylene glycol	GoLYTELY‡ (4 L)	\$12.30	\$14.55	\$25.49
Sodium picosulphate, citric acid and magnesium oxide	Pico-Salax§ (two sachets)	\$12.60	\$12.69	\$22.99

*Hospital costs are based on the Sir Mortimer B Davis – Jewish General Hospital and McGill University Health Centre, Montreal, Quebec. Retail costs and suggested retail prices are based on the distribution centre of Shoppers Drug Mart Canada. *Rougier Pharma, Canada; †Johnson & Johnson – Merck Consumer Pharmaceuticals of Canada; ‡Braintree Laboratories Inc, Canada; §Ferring Pharmaceuticals Inc, Canada*

TABLE 2
Randomized comparisons of sodium phosphate (NaP) versus polyethylene glycol (PEG) bowel preparations for colonoscopy

Reference	n	Preparation	Efficacy	Tolerability and acceptability
Vanner et al (14)	102	NaP PEG	NaP > PEG	NaP > PEG
Kolts et al (15)	72	NaP PEG	NaP > PEG	NaP = PEG
Marshall et al (16)	143	NaP PEG	NaP = PEG	NaP = PEG
Cohen et al (17)	422	NaP PEG	NaP > PEG	NaP > PEG
Golub et al (18)	230	NaP PEG	NaP = PEG	NaP > PEG
Henderson et al (19)	242	NaP PEG	NaP = PEG	NaP > PEG
Thomson et al (20)	116	NaP PEG	NaP = PEG	NaP = PEG
Clarkston et al (21)	98	NaP PEG	NaP = PEG	NaP = PEG
Frommer (22)	486	NaP PEG	NaP > PEG	NaP ≥ PEG
Lee et al (23)	209	NaP PEG	NaP = PEG	NaP = PEG
Arezzo (24)	300	NaP PEG	NaP > PEG	NaP > PEG
Kastenberg et al (25)	845	NaP tablets PEG	NaP tablets = PEG	NaP tablets > PEG
Law et al (26)	299	NaP PEG	NaP > PEG	NaP > PEG
Seinela et al (27)	72	NaP PEG	NaP = PEG	NaP = PEG
Hwang et al (28)	80	NaP PEG	NaP = PEG	NaP = PEG
Ell et al (29)	126	NaP PEG	PEG > NaP	PEG ≥ NaP
Hookey et al (30)*	171	NaP + bisacodyl PEG	PEG > NaP + bisacodyl	NaP + bisacodyl > PEG
Young et al (31)	323	NaP PEG + bisacodyl	NaP > PEG + bisacodyl	NaP > PEG + bisacodyl
Afridi et al (50)	147	NaP + bisacodyl PEG	NaP + bisacodyl = PEG	NaP + bisacodyl > PEG

*Low dose (1×45 mL) of NaP

TABLE 3
Randomized comparisons of various administration strategies of polyethylene glycol (PEG) bowel preparations for colonoscopy

Reference	n	Preparation	Efficacy	Tolerability and acceptability
Wang and Lin (33)	104	PEG Bisacodyl	PEG = bisacodyl	PEG = bisacodyl
Radaelli et al (34)	283	PEG Senna	Senna > PEG	Senna = PEG
Clarkston and Smith (35)	114	PEG PEG + bisacodyl	PEG + bisacodyl > PEG	PEG = PEG + bisacodyl
Ziegenhagen et al (36)	120	PEG PEG + senna	PEG + senna > PEG	PEG = PEG + senna
Sharma et al (37)	80	PEG + Mg-citrate PEG	PEG + Mg-citrate > PEG	PEG + Mg-citrate > PEG
Hookey et al (38)	171	PEG 4 L PEG 2 L + senna	PEG 4 L > PEG 2 L + senna	PEG 2 L + senna > PEG 4 L
Sharma et al (39)	150	PEG 4 L PEG 2 L + Mg-citrate PEG 2 L + bisacodyl	PEG 2 L + Mg-citrate, PEG 2 L + bisacodyl > PEG 4 L	PEG 2 L + Mg-citrate > PEG 2 L + bisacodyl ≥ PEG 4 L
Adams et al (40)	382	PEG 4 L PEG 2 L + bisacodyl	PEG 2 L + bisacodyl = PEG 4 L	PEG 2 L + bisacodyl = PEG 4 L
DiPalma et al (41)	200	PEG 4 L PEG 2 L + bisacodyl	PEG 2 L + bisacodyl = PEG 4 L	PEG 2 L + bisacodyl > PEG 4 L
Huppertz-Hauss et al (42)	231	PEG 4 L PEG 2 L + bisacodyl NaP	NaP = PEG 2 L + bisacodyl = PEG 4 L	NaP = PEG 2 L + bisacodyl = PEG 4 L
Hangartner et al (43)	300	PEG 4 L PEG 2 L + PSMC Senna + enema	PEG 4 L > senna + enema > PEG 2 L + PSMC	Senna + enema > PEG 4 L, PEG 2 L + PSMC
Borkje et al (44)	183	PEG 4 L PEG 1.5 L + PSMC	PEG 4 L = PEG 1.5 L + PSMC	PEG 4 L = PEG 1.5 L + PSMC
Aoun et al (45)	141	PEG 4 L + liquid diet PEG 2 L (×2) + regular diet	PEG 2 L (×2) + regular diet > PEG 4 L + liquid diet	PEG 2 L (×2) + regular diet = PEG 4 L + liquid diet
El Sayed et al (46)	187	PEG 3 L + liquid diet PEG 2 L + bisacodyl + regular diet + PEG 1 L	PEG 2 L + bisacodyl + regular diet + PEG 1 L > PEG 3 L + liquid diet	PEG 2 L + bisacodyl + regular diet + PEG 1 L > PEG 3 L + liquid diet

Mg-citrate Magnesium citrate; NaP Sodium phosphate; PSMC Sodium picosulphate plus Mg-citrate

an iso-osmotic solution and is preferred in patients with significant cardiac or renal disease.

NaP

As mentioned above, sixteen trials (14-29) compared PEG with NaP (Table 2). NaP was superior to PEG in efficacy in six of 16 trials, and was superior in tolerability and acceptability in seven of 16 trials. Only two trials (29,30) suggested that PEG was superior to NaP with regards to efficacy. NaP was more effective and equally tolerated compared with PSMC in two studies (47,48), while in a third study, the two preparations were equally effective but PSMC was better tolerated (Table 4) (49).

Bisacodyl did not appear to increase the efficacy of NaP – the combination was equal to or less effective than PEG (30,50) – but the combination of bisacodyl and NaP was better tolerated than PEG. The ingestion of a carbohydrate-electrolyte solution (Gatorade, PepsiCo Inc, USA or E-lyte, BodyBio Inc, USA) to counteract the fluid and electrolyte shifts of NaP further increased efficacy and either improved or did not affect tolerability and acceptability compared with NaP alone (Table 5)

(51,52). The addition of the carbohydrate-electrolyte solution resulted in less intravascular volume contraction, hypokalemia and the need for intravenous rehydration. In one study (53), using NaP with a liberalized diet (light lunch after a light breakfast) was equally effective and tolerated compared with NaP plus a clear liquid diet. However, no study to date has determined whether a regular breakfast may be allowed.

Strategies for additional preparation in the case of inadequate bowel cleansing may vary from centre to centre. However, clinicians are cautioned not to use higher than the standard NaP dosing regimens in patients with an initial poor preparation.

PSMC

In terms of efficacy, PSMC was more effective (11), less effective (54) and equivalent to (55) PEG in three controlled trials (Table 4). PSMC was better tolerated in all three trials (Table 4). Two of three trials (47,48) demonstrated superior efficacy of NaP over PSMC with no difference in tolerability and acceptability, while in the third trial (49) that used a higher

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TABLE 4
Randomized comparisons of sodium picosulphate plus magnesium citrate (PSMC) bowel preparations for colonoscopy

Reference	n	Preparation	Efficacy	Tolerability and acceptability
Regev et al (11)	68	PSMC	PSMC > PEG	PSMC > PEG
Chilton et al (32)	132	PEG 1 L + PSMC + senna NaP	PEG 1 L + PSMC + senna > NaP	Not reported
Hangartner et al (43)	300	PEG 2 L + PSMC PEG 4 L Senna + enema	PEG 4 L > senna + enema > PEG 2 L + PSMC	Senna + enema > PEG 4 L, PEG 2 L + PSMC
Borkje et al (44)	183	PEG 1.5 L + PSMC PEG 4 L	PEG 4 L = PEG 1.5 L + PSMC	PEG 4 L = PEG 1.5 L + PSMC
Yoshioka et al (47)	103	PSMC NaP	NaP > PSMC	PSMC = NaP
Tjandra et al (48)	225	PSMC NaP	NaP > PSMC	PSMC = NaP
Schmidt et al (49)*	400	PSMC NaP	PSMC = NaP	PSMC > NaP
Dakkak et al (54)	59	PSMC PEG	PEG > PSMC	PSMC > PEG
Hamilton et al (55)	55	PSMC PEG	PSMC = PEG	PSMC > PEG

*High dose (three sachets) of PSMC. NaP Sodium phosphate; PEG Polyethylene glycol

TABLE 5
Randomized comparisons of the use of carbohydrate-electrolyte (carb/electrolyte) solutions or diets with sodium phosphate (NaP) bowel preparations for colonoscopy

Reference	n	Preparation	Efficacy	Tolerability and acceptability
Barclay et al (51)	168	NaP NaP + carb/electrolyte	NaP + carb/electrolyte > NaP	NaP + carb/electrolyte = NaP
Tjandra and Tagkalidis (52)	187	NaP NaP + carb/electrolyte	NaP + carb/electrolyte > NaP	NaP + carb/electrolyte > NaP
Scott et al (53)	200	NaP NaP + diet liberalization	NaP = NaP + diet liberalization	NaP = NaP + diet liberalization

Carb/electrolyte solutions were Gatorade (PepsiCo Inc, USA) or E-lyte (BodyBio Inc, USA)

dosage of PSMC, the two preparations were equally effective but PSMC was better tolerated (Table 4). When PSMC was used in combination with low-volume PEG (1.5 L or 2 L), the combination was equally or less effective than PEG 4 L with no improvement in tolerability and acceptability (43,44). A low-dose, low-volume triple regimen of PSMC, PEG 1 L and senna was more effective than NaP (32). The clinical experience of many of the CAG committee members suggests that the amount of fluid intake is critical to the quality of preparation with PSMC.

Mg-citrate

In patients undergoing colonoscopy, Mg-citrate and bisacodyl was more effective and better tolerated than castor oil (Table 6) (56). When used alone or in combination with bisacodyl and a diet kit, Mg-citrate was as or more effective than NaP (57,58), but tolerability and acceptability were greater only with the combination of Mg-citrate, bisacodyl and a diet kit. As in studies with PEG (45,46), and NaP (53), it may be possible to relax the need for dietary restrictions. A low-residue diet kit combining Mg-citrate and bisacodyl was more effective and better tolerated than NaP with a standard clear liquid diet (58). Mg-citrate

added to a low-volume PEG preparation improved patient tolerability without sacrificing efficacy of colon cleansing compared with the standard PEG 4 L (37,39).

SAFETY

All bowel preparations may cause adverse events. The clinician must be aware of the patient's comorbidities and be familiar with the adverse events profile and recommended modes of administration when selecting a preparation.

A review of NaP and PEG studies conducted in 2002 assessed the rate of adverse events reported to major government institutions (59). Between 1997 and 2002, the United States Food and Drug Administration (FDA) received 100 reports of adverse events with PEG solutions, including 30 serious and six fatal events (59). Between the same time period, the United States FDA received 34 adverse event reports related to oral NaP solutions, 18 of which were serious events, including eight fatalities (59). A review of published case reports (59) suggested that definite or probable predisposing factors were identifiable in 10 of 13 patients with severe adverse events. However, three patients had no identifiable predisposing factors. In all identifiable

TABLE 6
Randomized comparisons of magnesium citrate (Mg-citrate) bowel preparations for colonoscopy

Reference	n	Preparation	Efficacy	Tolerability and acceptability
Sharma et al (37)	80	Mg-citrate + PEG PEG	Mg-citrate + PEG > PEG	Mg-citrate + PEG > PEG
Sharma et al (39)	150	PEG 4 L PEG 2 L + Mg-citrate PEG 2 L + bisacodyl	PEG 2 L + Mg-citrate, PEG 2 L + bisacodyl > PEG 4 L	PEG 2 L + Mg-citrate > PEG 2 L + bisacodyl ≥ PEG 4 L
Chen et al (56)	70	Mg-citrate + bisacodyl Castor oil	Mg-citrate + bisacodyl > castor oil	Mg-citrate + bisacodyl > castor oil
Berkelhammer et al (57)	297	Mg-citrate NaP	Mg-citrate ≥ NaP	NaP > Mg-citrate
Delegge and Kaplan (58)	506	Mg-citrate + bisacodyl + diet kit NaP + liquid diet	Mg-citrate + bisacodyl + diet kit > NaP + liquid diet	Mg-citrate + bisacodyl + diet kit > NaP + liquid diet

NaP Sodium phosphate; PEG Polyethylene glycol

serious adverse events, inappropriate dosing, inappropriate patient selection or inadequate hydration could be identified as predisposing factors.

Spontaneous adverse reactions reported to the Canadian Adverse Drug Reaction Monitoring Program as of September 2005 included 38 reports with oral NaP, 18 reports with PEG, 31 reports with Mg-citrate and one report with PSMC (60), keeping in mind that PSMC has only been made available in Canada since 2005. From May 1997 to October 2001, Health Canada received 10 reports of suspected adverse reactions to oral NaP, nine of which were serious and none were fatal (61). Five patients had electrolyte disturbances, including hypocalcemia and hyperphosphatemia, four of whom had a medical history of renal insufficiency, cardiovascular disease or concomitant use of medications that affected electrolytes. At least four of the 10 patients ingested more than 45 mL of NaP within a 24 h period.

Because of concerns with the NaP preparation, both the United States FDA and Health Canada recommended a 'black box advisory' against the use of more than 45 mL of oral NaP within 24 h (62). However, experience from clinical trials where 90 mL of NaP was used within 24 h suggests that this dosing may be suitable in some cases; in fact, many members of the CAG expert panel administer this dosing schedule after careful one-on-one discussion of risks and benefits in carefully selected patients.

There is more experience with PSMC in the United Kingdom, and between 1995 and 2001, Ferring Pharmaceuticals Ltd, United Kingdom, described 21 reported adverse events, including five serious events of hyponatremia and no fatalities (63). In addition, in 2002, the Australian Adverse Drug Reactions Advisory Committee described 16 reports of serious adverse events with PSMC with no fatalities (64).

PEG

As with any oral preparation, PEG is contraindicated in patients with ileus, gastric retention, bowel perforation, gastrointestinal obstruction or severe colitis (65). Due to its iso-osmolality, PEG appears to be relatively safe for patients with electrolyte imbalance and those who cannot tolerate a significant fluid load (renal failure, congestive heart failure [CHF] or advanced liver disease with ascites) (66).

In studies comparing PEG with NaP, decreases in systolic blood pressure of over 10 mmHg were noted in more patients treated with PEG in one study (45% versus 28%) (50) and fewer patients in another (7% versus 16%) (14); however, these differences were not statistically significant. In one study (50), a significantly higher number of patients experienced a 20 mmHg drop in systolic blood pressure with PEG compared with NaP (25% versus 12%, $P=0.05$).

Rare adverse events reported with PEG include pulmonary aspiration, Mallory-Weiss tear, pancreatitis and colitis, cardiac dysrhythmia and inappropriate antidiuretic hormone syndrome (67-70). A mild, asymptomatic increase in plasma volume may occur (71), and one case of exacerbation of CHF in a patient with CHF and chronic renal insufficiency has been reported (72).

Three cases of serious dysnatremia were reported: one in a patient taking thiazide diuretics who presented with seizures and recovered, and two fatal cases in patients with end-stage renal disease (73).

PEG has not been shown to alter the histological features of the colonic mucosa and may be used in patients suspected of having inflammatory bowel disease (IBD) without interfering with the diagnosis (74).

NaP

Because oral NaP may cause fluid and electrolyte shifts, it is contraindicated in patients with kidney disease or those on a sodium-restricted diet (65); it should not be used in patients with CHF or advanced liver disease (8,59), and should be used with caution in elderly patients and patients with small intestinal disorders and with poor gut motility (8). As with any oral preparation, NaP should not be used in patients with bowel obstruction.

In a review of 26 studies (59), there were no major adverse events due to NaP; however, it is important to note that patients with renal failure, ascites, serious heart disease and bowel obstruction were excluded from these trials. Most patients receiving NaP have transient hyperphosphatemia, more so in the elderly. Concerns have been expressed about a reciprocal decrease in serum calcium levels. The meta-analysis also reported on serum calcium levels in 654 patients in 12 trials (59). Most studies showed a small decrease in mean serum

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calcium levels, with a few cases below the normal calcium limit, but not in the range that would cause symptoms. Up to 20% of patients using NaP preparations developed hypokalemia (59,75). Increases in sodium levels are generally small and do not lead to clinical sequelae (59); however, significant hyponatremia and seizures have been reported (76). Care must be taken in patients with a low seizure threshold and those with possible chronic sodium depletion, such as patients on thiazide diuretics.

In clinical trials, body weight, urine osmolality and serum sodium showed a trend toward minor intravascular volume contraction, but no correlation with symptoms attributable to the colonoscopy preparation was reported (59). The risk of clinically significant volume contraction and dehydration may be lessened by encouraging patients to drink clear fluids liberally during the days leading up to the procedure, especially during preparation (77).

In the meta-analysis (59), hemodynamic measurements were available from five studies, in 405 patients receiving NaP. Decreases in blood pressure of over 10 mmHg were noted in 16% to 28% of patients, and over 20 mmHg in 12% to 16% of patients. Studies that compared NaP with PEG found no significant differences (14,20,77) or a greater drop in blood pressure with PEG (50).

In December 2005, Health Canada issued an advisory regarding the safety of NaP, due to concerns about nephrocalcinosis associated with renal failure (78). In addition to published reports of seven cases (79-81), an additional 30 cases of acute renal failure involving calcification of renal tissue have been spontaneously reported (78). Some of the cases appear to have involved inappropriate patient selection, as well as overdosing and NaP use in patients at higher risk of dehydration (eg, elderly and debilitated patients). In the published reports, six of seven patients were hypertensive, with five on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and two also on diuretics. One patient had a relative contraindication (hyperparathyroidism) to the use of the product and another patient was given an overdose. A cohort study (82) suggested that the prevalence of the development of renal failure with NaP and PEG groups was similar (7% versus 9%, respectively), and that only age and blood pressure, independently, predicted renal failure regardless of the preparation used. Despite limitations, these data suggest that inadequate hydration, older age, hypertension and the use of diuretics and antihypertensives, and perhaps coronary artery disease may increase the risk of renal dysfunction in patients receiving NaP cleansing preparation, further emphasizing that precautions are required in these situations.

NaP has been shown to alter both the macroscopic and the microscopic features of the intestinal mucosa, and induce aphthoid erosions similar to those seen in IBD, thus confusing the colonoscopic appearance (83-86).

An anhydrous form of NaP sold as tablets in the United States remains unavailable in Canada.

PSMC

PSMC is contraindicated in patients with CHF, gastric retention, gastrointestinal ulceration, ileus, toxic colitis, gastrointestinal obstruction or perforation, or severely impaired renal function, and should be used with caution in patients with renal impairment, heart disease, IBD, patients on concomitant medications that affect electrolyte balance (eg, diuretics), and in elderly or debilitated patients (65).

Few data are available on the biochemical and hemodynamic effects of PSMC. In one study (55), PEG was associated with significant decreases in potassium levels, while PSMC was associated with significant decreases in chloride levels and significant increases in magnesium levels. In another study (47), there were no significant changes in hemoglobin, hematocrit, sodium, potassium, phosphate, calcium, urea or albumin levels with PSMC, compared with a significant increase in phosphate levels with NaP (47). However, significant dehydration and electrolyte abnormalities have been described (64). The 16 Australian adverse reports (64) implicating PSMC, described by the Adverse Drug Reactions Advisory Committee, included eight reports of adverse events (ie, convulsions, syncope, unconsciousness and metabolic alkalosis) associated with hyponatremia, as well as four reports of syncope and dehydration without documented electrolyte abnormalities. Electrolyte abnormalities resulting in seizures have been reported in a patient using PSMC (76).

Two studies (87,88) have reported that PSMC was used safely and effectively in patients with IBD; however, neither study assessed the impact on histological results.

Mg-citrate

Mg-citrate is contraindicated in patients with abdominal pain or hemorrhage, intestinal obstruction or impaired renal function, and should be used with caution in patients on a low-sodium diet (65). The major route of Mg-citrate excretion is renal, and severe or even fatal episodes of hypermagnesemia have been reported in patients with suspected or known renal failure or elderly patients (89,90). Electrolyte abnormalities resulting in seizures have been reported in a patient using PSMC (76).

EFFICACY AND TOLERABILITY IN PEDIATRIC POPULATIONS

Unlike studies in adults, there are very few studies actually evaluating and/or comparing the various methods used to prepare the colon for colonoscopy in infants or younger children. Most bowel preparation strategies are simply adapted from those used in adult patients; however, this may not always be appropriate. Compliance is often the first obstacle in children. The choice of preparation will be affected by the patient's age, taste of the medication, volume to be consumed and product formulation (pill versus liquid). Often children require admission to a day procedure unit and administration of the bowel cleansing preparation via a nasogastric (NG) tube. The data on safety and side effects in children are also limited.

PEG electrolyte solution was assessed in 20 children (1.5 to 19 years of age) and found to provide adequate colon cleansing, but 55% of children required an NG tube to take the solution (91). The majority of children had significant discomfort taking the solution. There were also minor changes in urine osmolality, urea, serum glucose and potassium levels. Two other studies (92,93) comparing lavage solution with oral NaP in 63 children (three to 17 years of age) found that children tolerated the oral NaP better, but hyperphosphatemia occurred in both studies (Table 7). A prospective trial (94) reported 46 children (2.8 to 17.8 years of age) who were given PEG 2 L in a beverage, divided into two to three doses, for four days. Patients went from an average of 2.5 stools/day to six stools/day before colonoscopy. Overall the preparation was successful. There were no comments on the ability of children to go to school or to participate in activities, especially with five to six stools/day. No patients

TABLE 7
Randomized comparisons of bowel preparations for colonoscopy in children

Reference	n	Preparation	Efficacy	Tolerability and acceptability
Gremse et al (92)	34	NaP PEG	NaP > PEG	NaP > PEG
da Silva et al (93)	29	NaP PEG	Not reported	NaP > PEG
Dahshan et al (95)	70	PEG Mg-citrate Bisacodyl + enema	PEG > Mg-citrate > bisacodyl + enema	Mg-citrate = bisacodyl + enema > PEG
El-Baba et al (96)	62	NaP Mg-citrate + bisacodyl + diet kit	Mg-citrate + bisacodyl + diet kit > NaP	Mg-citrate + bisacodyl + diet kit > NaP
Pinfield and Stringer (97)	66	PSMC Bisacodyl + enema	PSMC > bisacodyl + enema	PSMC > bisacodyl + enema

Mg-citrate Magnesium citrate; *NaP* Sodium phosphate; *PEG* Polyethylene glycol; *PSMC* Sodium picosulphate plus *Mg-citrate*

appeared dehydrated but there were small but significant decreases in serum potassium, carbon dioxide and urea levels, although all still remained in the normal range with respect to age.

An RCT compared three combination bowel cleansing preparations in 77 children (three to 20 years of age): Mg-citrate and senna with clear liquid diet for two days; bisacodyl daily for two days; and PEG (20 mL/kg) and clear liquid diet at home on the day before colonoscopy, and NaP enema the day of colonoscopy (95). The PEG preparation provided the best cleansing but was the least well-tolerated with the greatest incidence of reported side effects (vomiting and poor sleep). The bisacodyl preparation was the best tolerated but provided significantly worse bowel cleansing. Electrolyte levels and hydration status were not assessed.

In another trial (n=62, mean age 12.5 years), bisacodyl in combination with Mg-citrate and a low-residue diet (prepackaged) was compared with two doses of NaP and a clear liquid diet administered the day before the procedure (96). Bowel cleansing was more effective with the combination of bisacodyl and Mg-citrate. Reported side effects were high in both groups (83% with bisacodyl and 100% with NaP), but only examined complaints such as headache, bloating, sleep disturbance and anal irritation. Safety data were not gathered.

Three studies (97-99) have reported on the combination of an oral laxative and enemas. An RCT of 63 children (18 months to 16 years of age) compared PSMC and a clear liquid diet with a bisacodyl and NaP enema combination and an unrestricted diet up to 6 h before colonoscopy (97). The PSMC regimen included two doses adjusted for weight and age, one at 24 h pre-endoscopy and the second at 18 h. One hundred per cent of patients from the PSMC group had a good or excellent preparation compared with 71% of patients from the bisacodyl and NaP enema combination group. An open study (98) evaluating oral bisacodyl for two days and a NaP enema in 30 children, reported excellent efficacy in 86% of children. No safety data were gathered. A second open study (99) compared various combinations of liquid diet, senna or Mg-citrate and one or two NaP enemas up to 48 h before the procedure. Although the authors thought that the preparations were adequate, the majority of children still had either liquid or semiformal stool at the time of the procedure. Again, no safety data were obtained.

All of the regimens have some downsides. In general, lavage solutions are effective if an adequate dose may be administered

but are often not well tolerated and need to be given via an NG tube. Oral NaP solution causes increases in serum phosphate levels, as are seen in adults. Whether low-volume PEG mixed in multiple glasses of fluid (carbohydrate-electrolyte solution, eg, Pedialyte, Abbott Laboratories Ltd, Canada) may be given safely over a shorter time period, with similar results, remains to be seen. Results with PSMC look promising, but there are no safety data looking at either electrolyte or hydration issues. Given the lack of adequate data assessing both efficacy and safety, it is difficult to recommend any one regimen for adequate bowel preparation in children.

Similar to the process in adults, all regimens need to ensure adequate hydration, especially in younger patients. It is important to remember that although sports drinks may be used as a 'hydration drink' in adults undergoing colonoscopy preparation protocols, the salt to sugar ratio is not appropriate for younger children. A carbohydrate-electrolyte solution designed for pediatric populations, such as Pedialyte, may be useful. Parents should be given guidelines to follow to ensure children stay adequately hydrated during the preparation period, which hopefully may be contained within 24 h. In addition, infants and children often become irritable and cry when placed on a clear fluid diet and/or a restricted diet. Parents have difficulty coping with this, and prolonging dietary restrictions while giving unpalatable medications may be near impossible to achieve. Further studies are needed to look at feasibility and efficacy, as well as safety, of various colonoscopy preparation protocols in children.

ROLE OF BOWEL CLEANSING PREPARATIONS IN CAPSULE ENDOSCOPY

In an effort to improve visibility of the distal small intestine in capsule endoscopy, several studies (100-106) have assessed PEG (in varying volumes), NaP and simethicone for bowel cleansing before the ingestion of the wireless device. Bowel preparation may change small bowel transit time (100-104) and visibility (102,105,106), which may lead to a higher rate of complete capsule endoscopy studies (102) and a higher diagnostic yield (103). While bowel cleansing before capsule may be useful, its routine use, let alone what preparation to use, remains the subject of ongoing debate (107).

It has been suggested that NaP may not be the best choice because of its propensity to induce erosions (83-86). It is possible

TABLE 8
The Canadian Association of Gastroenterology summary recommendations for bowel cleansing preparations

- Effective bowel preparations are critical to a high-quality colonoscopy examination and successful screening or surveillance programs of colonic pathology.
- All preparations can cause adverse events, including rare serious negative outcomes.
- NaP preparations appear more effective and better tolerated than standard PEG solutions.
- Regimens of PEG 2 L with bisacodyl (10 mg to 20 mg) or Mg-citrate (296 mL) are as effective as standard PEG 4 L regimens but are better tolerated and, therefore, may be the PEG regimens of choice.
- The efficacy of PSMC appears to be very good with excellent tolerability; head-to-head trials with NaP solutions are few and conclusions regarding comparative efficacy remain equivocal.
- Adequate hydration during preparation and up to the time of colonoscopy is critical to minimizing side effects in patients receiving NaP solutions, and probably PSMC preparations. Better hydration may also improve the quality of the bowel preparation.
- The Health Canada recommended dosing of NaP is 90 mL given as two 45 mL doses 24 h apart; however, in most clinical trials, the NaP dosing strategy was two 45 mL doses within 24 h. Many members of our expert panel administer both doses within 24 h, with one of the doses on the morning of the procedure, after careful one-on-one discussion of risks and benefits in carefully selected patients. Carbohydrate-electrolyte solutions may improve the efficacy and tolerability compared with NaP alone.
- The use of NaP preparations should be limited to patients without cardiac or renal dysfunction, bowel obstruction and ascites, and caution should be exercised when administering to patients with pre-existing electrolyte disturbances, patients taking medications that can affect electrolyte levels and elderly or debilitated patients.
- Safety data on PSMC and combination preparations in North America are limited and clinicians are encouraged to keep abreast of developments in this area.
- The Canadian Association of Gastroenterology urges its members, as always, to weigh the benefits and risks of the administration of any medications or compounds, including bowel cleansing preparations, on an individual basis.

Mg-citrate Magnesium citrate; NaP Sodium phosphate; PEG Polyethylene glycol; PSMC Sodium picosulphate plus Mg-citrate

that these erosions may be misinterpreted in a capsule study, but this has not yet been demonstrated in studies. The use of a cathartic resulting in an unpleasant preparation has the disadvantage of removing some of the simplicity of the capsule test which is viewed as a noninvasive, painless study by many people.

CONCLUSIONS

Effective bowel preparations are critical to a high-quality colonoscopy examination and successful screening or surveillance programs of colonic pathology. Table 8 lists the CAG recommendations relating to these preparations.

All preparations have been associated with adverse events, including lethal outcomes. Although NaP preparations appear more effective and better tolerated than PEG solutions, their use should be limited to patients without cardiac or renal

dysfunction, and caution should be exercised when they are administered to patients with pre-existing electrolyte disturbances, patients using medications that result in electrolyte disturbances and elderly or debilitated patients. A recent advisory recommended the administration of the full NaP preparation over two days. Adequate hydration is critical to minimizing side effects in patients receiving NaP, and probably PSMC preparations. Additionally, adequate consumption of clear fluids is essential to maintain any remaining effluent in the bowel in a fluid state so that it may be readily suctioned. The efficacy of PSMC appears to be very good but comparative trials with NaP are lacking and the preliminary conclusions equivocal. It may be best tolerated when compared with NaP and PEG preparations. There are few data on Mg-citrate because it is rarely used alone in preparation for colonoscopy.

The CAG urges its members, as always, to weigh the benefits and risks of the administration of any medications or compounds, including bowel cleansers, on an individual basis, and to keep abreast of evolving literature in this important area.

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