Tolerability, safety, and efficacy of sodium phosphate preparation for colonoscopy: The role of age

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RESUMEN

Objetivos: comparar la tolerancia subjetiva y los efectos adversos secundarios a la preparación para colonoscopia con dos productos, polietilenglicol (PEG) y fosfato de sodio (NaP), en pacientes adultos y en aquellos de 65 años o más.

Material y métodos: estudio retrospectivo apareado, tras escoger aleatoriamente a 140 pacientes de todos los que se sometieron a colonoscopia entre marzo de 2004 y mayo de 2005. Se investigó la presencia de los siguientes efectos adversos durante la preparación para la colonoscopia: fiebre, rectorragia, dolor abdominal, dolor perianal, náuseas, vómitos, sed, somnolencia, agitación, temblores y convulsiones. Se consideró mala tolerancia objetiva si el paciente presentó uno o varios de estos efectos. Asimismo, se recogió la tolerancia subjetiva al proceso de limpieza.

Resultados: se incluyeron 70 pacientes preparados con PEG y 70 pacientes con NaP (69 mujeres y 71 hombres, con edad media de 60,6 ± 14,8 años). No se demostró relación entre la tolerancia subjetiva o la presencia de efectos adversos y la limpieza con uno de los dos productos, ni en la población general ni en los pacientes de 65 años o más (p = 0,09 y p = 0,45 en los ancianos, respectivamente). A pesar de ello, los pacientes preparados con NaP presentaron más náuseas que los tratados con PEG (p < 0,009), sobre todo las mujeres de 65 años o más. No se observaron efectos adversos graves en los pacientes preparados con NaP. Los ancianos toleraron mejor cualquiera de las dos preparaciones mientras que las mujeres toleraron peor que los hombres la preparación, independientemente del producto empleado. La probabilidad de no completar la limpieza fue mayor en el grupo preparado con PEG y la calidad de ésta fue mejor en los que emplearon NaP.

Conclusiones: la preparación previa a colonoscopia con NaP es tan bien tolerada, segura y eficaz como la realizada con PEG, también en pacientes ancianos sanos, a pesar de producir más náuseas. La limpieza obtenida con NaP es de mejor calidad.


ABSTRACT

Objectives: to compare subjective tolerance and secondary adverse events to bowel cleansing prior to colonoscopy with polyethylene glycol (PEG) and sodium phosphate (NaP) in adult patients and in those 65 or more years old.

Material and methods: retrospective matched study, choosing 140 patients among all of those who underwent colonoscopy from March 2004 to May 2005. We investigated the presence of the next adverse events during bowel preparation: Fever, low digestive bleeding, abdominal pain, perianal pain, nausea, vomiting, thirst, somnolence, agitation, tremor and convulsions. We considered bad objective tolerance if the patient presented any one of these effects. We also asked patients about subjective tolerance to preparation.

Results: seventy patients prepared with PEG and seventy with NaP were included (69 women and 71 men, mean age 60,6 ± 14,8 years). There was no relationship between subjective tolerance or the presence of adverse events and bowel cleansing with any of the products in general population or in elderly patients (p = 0,09 and p = 0,45 in the elderly). However, patients prepared with NaP showed more nausea than those who employed PEG (p < 0,009), overall women of 65 or more years old. There were no severe adverse events in patients prepared with NaP. Elderly showed better tolerance than younger patients, and women worst tolerance than men, irrespective of the lavage preparation employed. Patients prepared with PEG unfinished bowel cleansing more frequently than those with NaP. Cleanliness achieved with NaP was significantly better than that obtained with PEG.

Conclusions: bowel cleansing prior to colonoscopy with NaP is as well tolerated, safe and effective as with PEG, even in elderly healthy patients, although it causes more nausea. Cleanliness with NaP is better than that achieved with PEG.

Key words: Sodium phosphate. Polyethylene glycol. Elderly. Tolerance.
INTRODUCTION

Colonoscopy has currently become the standard method for colon examination because of its diagnostic accuracy, and also because it allows therapeutic procedures. For appropriate visualization of the colonic mucosa during colonoscopy, bowel cleansing is required (1-5).

The ideal colorectal cleansing product would be one that left no residual fecal material in patients, with no effects on the colonic mucosa and no side effects, and with a low cost (6). No product with all these characteristics has been developed yet.

During the last few years the product most commonly used for bowel cleansing prior to colonoscopy was polyethylene glycol (PEG), a nondigestible, nonabsorbable osmotic laxative. Each dose of PEG is composed of 17.73 g of powder with 15 g of polyethylene glycol 4,000, 365.25 mg of sodium chloride, 186.25 mg of potassium chloride, 1,408.5 mg of sodium sulfate, 420 mg of sodium bicarbonate, and 120 mg of sodium biphosphate. Because of its electrical neutrality and isosmolarity with plasma, PEG does not result in net absorption or excretion of water or electrolytes (2,3,6), and henceforth, when administered in large doses, does not produce relevant changes in patient water and electrolyte levels. However, due to the large amount of fluid that a patient needs to drink (usually 4 liters), it can cause nausea, vomiting, and abdominal discomfort, which frequently lead to non-compliance and subsequent inadequate bowel preparation (2.5-8).

Another product for colon preparation prior to colonoscopy was later introduced, sodium phosphate (NaP). It is a saline laxative composed of dehydrated monosodium phosphate and dodecahydrated disodium phosphate (24.4 and 10.8 g in every 45 ml, respectively), which thanks to its osmotic qualities draws plasma to the bowel lumen (2.6,8,9). One of its main advantages is that it requires a lower liquid intake versus the classic PEG preparation, and thus facilitates therapeutic compliance. However, due to its composition and large osmotic activity, it can cause hydric and ionic disturbances such as hyperphosphatemia, hypernatremia, hyperchloremia, hypopotasemia and hypocalcemia, sometimes severe and with relevant clinical effects (1.9-11). Thus, it is contraindicated in congestive heart failure, severe renal failure, liver cirrhosis with ascites, active inflammatory bowel disease (IBD), and in patients in whom absorption may be increased by megacolon, intestinal obstruction or ileus. Except for these cases, NaP has shown in different comparative studies an efficacy and safety profile similar to or better than that of PEG, with less than 1 case of severe adverse events per 1 million healthy population, and a tolerance at least as good as that of PEG (1-6,8,12,13). Also in our country, in a multicenter study, efficacy and safety were seen to be similar to those of PEG, but with a better tolerance (14).

These studies have evaluated several aspects that could determine tolerance to both preparations, but as far as we are concerned, there are only a few that have focused on tolerance and safety in elderly patients aged 65 years or older (15,16). In these two studies it was proven that NaP cleansing is as efficient as PEG cleansing, and also safe for the elderly group if avoided in patients with contraindications.

The aim of the present study is to find whether subjective tolerance to both preparations is different, and if elderly patients prepared with NaP show a larger amount of clinical adverse events. To that purpose we carried out a retrospective study with adult patients and elderly patients prepared with PEG and NaP using a 1:1 ratio.

MATERIAL AND METHODS

Patients included in this study were randomly selected from all those who underwent colonoscopy, either emergent or elective, at Department of Gastroenterology, University Hospital 12 Octubre (Madrid), between March 2004 and May 2005.

Prior to colonoscopy all patients were prepared with one of the two different regimens for bowel cleansing: a) 16 doses of PEG (Solución Evacuante Bohn®; Bohm Laboratories, Fuenlabrada, Madrid, Spain), 8 of them 48 hours prior to colonoscopy, the remaining 8 24 hours before, each dose diluted in 250 mL of water; b) Two 45-mL doses of NaP (Fosfosoda®; Casen-Fleet, Utebo, Zaragoza, Spain) to be administered at 13 p.m. and 21 p.m. the previous day in cases where colonoscopy was due in the morning, and at 18 p.m. the previous day and 9 a.m. of the test day when colonoscopy was due in the evening. Each dose of NaP was to be diluted by mixing it with 200-250 mL of water, and patients were encouraged to drink approximately two liters of liquid the day before colonoscopy. In both preparations patients followed a 24-hour liquid diet prior to colonoscopy, and they were administered enemas as required in order to achieve adequate bowel cleansing.

All patients were legally of age, and gave their written consent to colonoscopy.

Colonoscopies were performed by attending gastroenterologists or a gastroenterology fellow supervised by an attending gastroenterologist who graded the overall quality of the colonic cleansing as “good” (less than 20% of mucosa covered with liquid stool, which could be suctioned or washed away), “fair” (20 to 50% of the mucosa covered with liquid stool), “poor” (more than 50% of mucosa covered with liquid or semisolid stool), and “bad” (non-assessed colonoscopies due to high amount of solid stools). It was graded as “accurate” or “inadequate” —a fair, poor, or bad preparation.

To compare “objective” tolerability between PEG and NaP the following features were considered: Fever, low digestive bleeding, abdominal pain, perianal pain, nau-
sea, vomiting, thirst, somnolence, agitation, tremor, and convulsions. We considered “objective tolerance” to be bad if one of those adverse events occurred during preparation. We also asked patients about subjective tolerance along the process, which could be good, fair, poor or bad. Once colonoscopy was completed, data were collected through personal or telephone interviews in one month at most. Patients who did not co-operate or who could not be contacted were excluded.

For the statistical study we used the SPSS 11.0 for Windows and SAS programs. To compare proportions we employed the Chi squared test or Fisher’s test when needed, while for continuous variables we used Student’s t-test. In the same way a multivariate adjustment was performed using a logistical decline. The power of associations was calculated using odds ratios and 95% confidence intervals. A “p” value <0.05 was considered “significant”.

RESULTS

The study included 140 patients: 70 prepared with PEG and 70 with NaP. Sixty-nine of them (49.3%) were women, with mean patient age being 60.6 ± 14.8 years, range 18 to 84 years. Each group (PEG and NaP) was subdivided into two groups depending on age, one consisting of patients 64 years old or younger (38 prepared with PEG and 38 with NaP), the other group consisting of patients 65 years old or older (32 patients in each subgroup). Among patients prepared with PEG mean age was 60.7 ± 14.9 (95% CI: 57.2-64.3) and median age was 63; mean age of patients prepared with NaP was 60.5 ± 14.8 (95% CI: 57-64) with a median of 62 years (Table I).

Regarding sex distribution, NaP had an unbalance (41 men vs. 29 women) that was not statistically significant (p = 0.06) (Table I).

One hundred and eleven of all 140 patients participating in the study showed no relevant concomitant conditions, 17 were suffering from heart disease; 12 from respiratory disease, and 5 from liver disease. The most common indications for colonoscopy were polyps (24 cases in each group), low digestive bleeding (13 in the PEG group and 22 in the NaP group), suspected neoplasia (PEG 16, NaP 4), and constipation (PEG 7, NaP 11) (Table I).

From the point of view of diagnosis there was no organic colonic pathology in 43 (31%) patients, and the remaining 97 (69%) showed one or various of the following pathologies: Polyps (42%), diverticular disease (30%), IBD (5%), neoplasia (4%), and non-specific inflammatory changes (9%) (Table II).

Table II. Endoscopic diagnostic with every product (a patient can present more than one indication for the endoscopy)

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>PEG &lt; 65 years</th>
<th>≥ 65 years</th>
<th>NaP &lt; 65 years</th>
<th>≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Polyps</td>
<td>16</td>
<td>7</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>7</td>
<td>12</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>IBD</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>35</td>
<td>44</td>
<td>46</td>
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</tbody>
</table>

IBD: Inflammatory bowel disease.

Adverse events and subjective tolerance

In the separate analysis of adverse events there were no significant differences between both products except for the presence of nausea, which occurred in 19% of patients prepared with PEG vs. 39% of those prepared with NaP (p <0.009). As for age we reported no differences in the presence of nausea in the group below 65 years of age, but we could associate nausea and NaP preparation in patients over 65 (PEG: 6%; NaP: 28%; p = 0.02). However, when taking sex into account women had more nausea with NaP than with PEG (59 vs. 28%; p = 0.009), while that association could not be demonstrated in men (24 vs. 7%; p = 0.06).

In the overall analysis we found no differences, as 59% of patients prepared with PEG showed at least one of the aforesaid adverse events, against 66% of those prepared with NaP. There was no relationship between any of the two products and a higher presence of overall adverse events after dividing the patients into the aforesaid age groups (elderly, PEG: 41%; NaP: 50%; p = 0.45).

From the point of view of sex, while women had a higher number of total adverse events with NaP, 65 in 25 of the women prepared with NaP against 53 in 26 of those who were prepared with PEG (p = 0.01), we could establish no association between bad objective tolerance and colon preparation with the aforesaid product (PEG: 65%; NaP: 86%; p = 0.06). No differences were seen in men between both products.
Regardless of the product used, patients with age 64 or younger were the ones who showed the worst objective tolerance to preparation: 76% with at least one adverse event vs. 45% of those 65 years old or older (p = 0.0002), with an OR of 0.26 (95% CI: 0.12-0.53) favorable to the latter. Likewise women showed poorer objective tolerance when compared to men (74 vs. 51%, p < 0.005), with a higher presence of abdominal pain (p = 0.001), perianal pain (p = 0.001), and nausea (p < 0.002).

The subjective tolerance of patients to both preparations (PEG and NaP) was generally similar (p = 0.22). According neither to age (p = 0.09 in the elderly) nor to sex were significant differences found between both products.

However, irrespective of the product used, women showed a poorer subjective tolerance (p = 0.007), as 52% of them reported fair, poor, or bad tolerance vs. 34% of men. At the same time, only 30% of elderly patients reported fair, poor, or bad tolerance vs. 54% of patients at or younger than 64 years (p < 0.004).

Together with sex and age, we also studied some other features that could be relevant to objective and subjective tolerance to preparation. In the univariate analysis (regardless of the use of PEG or NaP) there was no relationship established between presence of comorbidity and at least one adverse event or poorer subjective tolerance. We could also observe no differences in objective or subjective tolerance related to the presence or absence of organic pathology during colonoscopy. Taking into account the cleansing product used, we observed no relationship between any of the two variables and tolerance, either objective or subjective.

In the multivariate analysis we observed that only age (OR: 3.7; 95% CI: 1.7-7.8) and sex (OR: 2.6; 95% CI: 1.2-5.6) influenced the presence of one or more of the adverse events during preparation, while we could not establish a relationship between comorbidity or endoscopic diagnosis and the aforesaid events. Regarding subjective tolerance we obtained similar results: Sex (OR: 2.1; 95% CI: 1.02-4.2) and age (OR: 3; 1.4-6.4) were related to bad tolerance.

Cleanliness

Bowel cleansing with NaP resulted in higher cleanliness vs. PEG (p = 0.007) since 66% of patients prepared with NaP obtained accurate cleansing vs. 47% of those who employed PEG (p < 0.03).

Patients prepared with PEG employed a mean of 2.5 ± 2.1 enemas against 1.7 ± 2.1 of those who employed NaP (no statistically remarkable differences).

Among those patients who did not complete the preparation we observed no differences in the quality of cleansing between both products, or between those who completed preparation, though in the latter case there is a tendency to better preparation with NaP (p = 0.06).

Patient compliance

Sixty-nine percent of patients prepared with PEG completed the regime against 90% of patients prepared with NaP (p < 0.002), being our conclusion that there was a higher probability of not completing the preparation in the case of PEG, with an OR of 4 (CI 95%: 1.6-10).

Considering age as a factor, 63 vs. 97% (p = 0.0006) of elderly patients (65 years and older) showed this difference, while we did not establish such difference among younger patients. As for the sex factor we conclude that women showed worse compliance of the PEG regime (63 vs. 93%, p < 0.004) while we did not observe such difference among men.

If we study the patients regardless of the preparation employed, we do not appreciate any relationship between a bad objective tolerance and a worse compliance of the cleansing regime, though we indeed observe a more frequent presence of vomiting among those who did not complete the preparation (p = 0.03). On the contrary, we could clearly establish a higher tendency of not completing the preparation among those patients that showed bad subjective tolerance (p < 0.02).

DISCUSSION

In this study we proved that in the general population the overall subjective tolerance to colonoscopy preparation and the presence of adverse events are similar with PEG or NaP. These data match most of the studies we reviewed, where tolerance to NaP cleansing was as good or better than with PEG (1-4,6,8,12-14,17,18).

When we studied the elderly group (patients 65 years of age and older), which was the aim of our study, we observed no significant differences in objective or subjective tolerance between both products, as the study by Thomson et al. also showed (16).

Nevertheless, we did establish a relationship between NaP preparation and presence of nausea among women with 65 years of age and older. The Frommer et al. study also showed a higher risk of nausea with NaP, but age or sex were not taken into account (7). Likewise, Seinelä et al. confirmed this relationship in a study carried out with patients 80 years of age and older, but without this sex ratio (15). Nausea could be caused by irritation of the gastric mucosa due to the high osmolality of the product (1,700 mOsm/l) (7). Bujanda et al. suggest that nausea could be diminished by taking a second glass of liquid after each of the doses, as that could reduce osmolality in the solution (5). On the contrary, we found no higher presence of vomiting or thirst in patients prepared with NaP, as others previously explained (7).

In our study we have not clearly demonstrated a relationship between bad objective tolerance and any of the two products if we consider sex a factor. However, we
observed that women showed worse subjective tolerance and a higher frequency of adverse events irrespective of the product employed. To our knowledge, these effects have not been proven before. These differences could be explained because women have a poorer tolerance to acute gastric strain by liquid, which is enhanced by a higher prevalence of functional dyspepsia in this sex (19), and this reduces even more the volume of ingested liquid without showing nausea or other gastric symptoms (20). This lower tolerance to ingested liquid may affect compliance with preparation and increase objective and subjective symptoms to preparation. Another possibility could be that these conclusions are due to the retrospective nature of the study, which may show that women remember better than men their preparation regimen.

It is highly remarkable that patients 65 years or older showed a better objective and subjective tolerance to preparation irrespective of the product employed. One of the factors may be an alteration in the sensitivity threshold in this population group, but this is difficult to prove because we found no related data in the studies we reviewed. Again we could think that maybe some patients forgot to mention some of the adverse events due to the retrospective design of the study, but this is not very likely because we specifically asked them about all of them throughout a personal interview.

Two further factors that, at least theoretically, may influence tolerance (subjective or objective) have also been studied, namely comorbidity and endoscopic findings, but we found no difference in tolerance, neither in the univariate nor in the multivariate analysis. With respect to comorbidity (heart, respiratory or liver disease), its low prevalence among patients included does not allow an accurate study, while in the case of organic colonic disease data may prove enough. We have not found any references regarding these factors in the studies we reviewed.

Regarding the product used, compliance with the cleansing regimen was not worse in patients with bad objective tolerance, “bad” being defined as at least one adverse event, but was influenced by subjective tolerance, and this suggests that it could consist of adverse events plus other functional elements. On the other hand, it is also understandable that patients with vomiting could not complete preparation in a number higher than that of those with no vomiting.

Nevertheless, taking the product into account we observed that women 65 years or older better complied with the preparation when NaP was used, and that was likely because it demanded less liquid ingestion (19,20). These data reach the same conclusion as some of the previous studies reviewed (1,2,8,18,21), although these studies did not take age or sex into consideration. The OR favoring NaP compliance is quite similar to the relative risk described in the Hsu et al. meta-analysis (2). On the contrary, in the study by Young et al., where the PEG regimen implied ingesting only two liters of liquid, compliance was much higher than in our study (13).

Regarding the better quality of cleansing obtained with NaP in our patients, it is likely due to better compliance with the preparation since, if we consider only those patients who completed the preparation, we found no significant differences between both products, even though there was a slightly better cleansing when NaP was employed. What is obvious is that the aforesaid difference has nothing to do with enemas, because they were employed more frequently by patients prepared with PEG. As they were aware of their worse preparation they increased their usage, but it was not statistically significant. In any case, we cannot forget that better colon cleansing increases diagnostic yield and reduces costs because fewer second colonoscopies are needed (2,12).

Other authors have also proven that colon cleansing is better with NaP (5,8,12,13), and some of them state that the probability of needing an extra colonoscopy due to presence of fecal material is higher in patients prepared with PEG (1,2). Only the Vanner et al. study (8) suggests a relationship between the poorer cleansing obtained with PEG and failure to complete the preparation regimen, while other studies do not consider the potential role of having completed or the preparation regimen or otherwise, and even exclude from the analysis patients who did not complete said regimen (4).

Other studies have also speculated over the importance of timing for product ingestion. Frommer et al. and other groups conclude that cleansing is better with NaP when the second dose is administered a few hours before colonoscopy (8,12), while there were no differences with PEG if both products were ingested on the day before colonoscopy (7,13,17). However, other studies did not show such differences between PEG and NaP using this regimen (18). The study by Ell et al. is remarkable in that it reaches the opposite conclusions. In this study both doses of NaP were administered the day before colonoscopy, and a second dose of PEG was administered on the morning of exploration, with the PEG preparation being the product that obtained better results (3). The great percentage of good or excellent cleansing in the aforesaid study (83%) does not match its equivalent in our study (47%), and that was likely because regimen compliance with PEG was far better in that population (3).

Although in our study no biochemical measurements were obtained, we have previously proven (22), as other works did, that healthy patients prepared with NaP present more frequently with ionic alterations than those prepared with PEG, but at the same time those alterations were rarely of clinical significance, even in the elderly (2,3,6,9,12,15,16,18). In fact, in our study only one patient (a 47-year-old woman) needed to be admitted to hospital after the procedure, and she had employed the PEG preparation. While potential side effects may involve the heart from ionic alterations, nobody has proven so far a greater frequency of cardiac arrhythmias while
preparing with both products (18). Beloosesky et al. concluded that for patients 65 years of age or older, NaP could cause severe ionic alterations (hyperphosphatemia, hypermagnesemia, and hypocalcemia, basically), but these effects were transient and without clinical significance. However, they did not compare this group with a group of similar characteristics that was prepared with PEG (9). In the papers we have reviewed we found some cases of symptomatic hypocalcemia after NaP preparation, one of them leading to death (10,11). In all of those cases there was either a product overdose involved or patients had associated medical risk factors such as renal failure, or both things. This confirms what we have explained so far regarding the safety of using the right dosage in patients without an adverse event profile.

To conclude, objective and subjective tolerance to both preparations (PEG and NaP) was similar in the general population and in patients 65 years and older, though patients prepared for colonoscopy with NaP showed nausea more frequently than those prepared with PEG, usually women 65 years of age and older. Objective and subjective tolerance was worse regardless of the product in patients below 65 years and in women. Patients who followed the NaP regimen completed it better than those who followed the PEG regimen, and this difference is also due to the group of women above 65 years of age, and they achieved better colon cleansing. Therefore, preparation with NaP is also safe and efficient in elderly patients without severe pathologies.

A randomized, prospective, controlled study is warranted to confirm these results, since some of them are different from what has been published so far or, to our knowledge, have not been studied before.

REFERENCES