The effect of polyethylene glycol electrolyte balanced solution on patients with acute colonic pseudoobstruction after the resolution of colonic dilation; a prospective, randomized, placebo-controlled trial.

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short title: PEG for the relapse of Ogilvie’s syndrome

Key words: acute colonic pseudoobstruction, Ogilvie’s syndrome, polyethylene glycol, constipation

abbreviations used in the present paper: PEG: polyethylene glycol

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ABSTRACT:

BACKGROUND AND AIMS: The conservative therapy of patients with acute colonic pseudoobstruction (Ogilvie’s syndrome) may be successful initially but relapses are common. The aim of the present study was to evaluate the effect of polyethylene glycol electrolyte balanced solution (PEG) on the relapse rate of the syndrome after initial resolution with neostigmine or endoscopic decompression.

PATIENTS AND METHODS: The study was performed on 30 consecutive patients who presented with abdominal distention and radiographic evidence of colonic dilation, with a caecal diameter $\geq 10$ cm, that resolved conservatively. Patients then were randomized to receive daily 29.5 gr PEG (n=15) or similar placebo (n=15). They were daily monitored for a 7-day period, for stool and flatus evacuations and colonic diameter on abdominal radiographs. The administration of the test solutions and the assessment of the patients’s symptoms and x-rays were performed in a blinded fashion. A caecal diameter $\geq 8$ cm with a concomitant $\geq 10\%$ increase after initial successful therapeutic intervention was considered as a relapse and these patients, after a second therapeutic intervention, were eligible to receive open-label PEG.

RESULTS: Twenty-five patients received neostigmine as initial therapeutic intervention which resulted in resolution of colonic dilation in 88% of cases. Eight patients had a successful endoscopic decompression. Five (33.3%) patients from the placebo group, had recurrent caecal dilation as compared with none of the patients in the PEG group (p=0.04). Therapy with PEG resulted in a significant increase in stool and flatus evacuations (p=0.001 and 0.032, respectively) as well as in a significant decrease in the diameter of caecum, ascending and transverse colon and abdominal circumference (p= 0.017, 0.018, 0.014 and 0.008, respectively).

CONCLUSIONS: The administration of PEG in patients with Ogilvie’s syndrome after initial resolution of colonic dilation may increase the sustained response rate after initial therapeutic intervention.
INTRODUCTION

Acute colonic pseudoobstruction (Ogilvie’s syndrome) is a rare disorder in which massive dilation of the colon develops without any mechanical obstruction. It usually occurs in hospitalized or institutionalized patients with serious underlying medical or surgical conditions (1). Even though the pathogenesis of the syndrome is not completely understood, the most popular theory supports an imbalance in autonomic innervation of the colon which leads to excessive parasympathetic suppression or sympathetic stimulation (1,2). It has been proposed that transient impairment of the sacral plexus may cause atony of the distal large bowel and functional obstruction with proximal dilation (3). This is supported by the observation in many patients that a cut-off at the splenic flexure is present on abdominal radiographs (3-5).

Ischemia and perforation are the feared complications of the syndrome. Spontaneous perforation has been reported in 3-15% of patients with a mortality rate of 50% or higher (6). The rate of ischemia and perforation rapidly increases when the duration of distention exceeds 6 days (3,7) whilst active intervention is required when caecal diameter exceeds 10 cm (8). In these cases neostigmine is considered to be the agent of choice (8). It has been shown that neostigmine induces a rapid resolution in up to 90% of cases (9,10). If there is no improvement after neostigmine administration an urgent endoscopic decompression with a tube placement is indicated (8,11). However, it is well documented that some patients experience an early recurrence after initial resolution with neostigmine or colonoscopic decompression. Even though there are no prospective trials, the rate of recurrence is estimated to be around 6-39% (2,10). These patients are particularly difficult to be managed since neostigmine may be less effective (9) and continuous endoscopic intervention carries significant risks.

In routine clinical practice many physicians prescribe osmotic laxatives after the resolution of colonic dilation in an effort to restore daily stool and flatus evacuations and to minimize the risks of early recurrence of the syndrome. To our knowledge, this approach has not been validated, yet. Polyethylene glycol electrolyte balanced solutions (PEG) are osmotic laxatives frequently used for the management of chronic functional constipation (12-14). PEG opposes the dehydration of bowel contents, leading to modification of stool consistency and increased faecal bulk. This, in turn, stretches muscle fibers in the bowel wall and probably triggers myogenic peristalsis. The increased retention of water in the colon lubricates and softens stools, and allows comfortable bowel action. PEG passes virtually unchanged through the whole gastrointestinal tract, including the colon. It is not metabolized, and its effect is not dependent on the state of the colonic microflora (15). It may also induce an acceleration of colonic transit through the left colon and the rectum (14). These effects of PEG may be of particular importance in patients with Ogilvie’s syndrome, after the resolution of colonic dilation.

In the present study we tried to evaluate prospectively the effect of PEG on patients with acute colonic pseudo-obstruction after the resolution of colonic dilation with neostigmine or colonoscopic decompression.

PATIENTS AND METHODS

Definitions and patient selection

During a 3-year period, patients were recruiting for the study from inpatient medical and surgical wards of Athens Naval and Veterans Hospital and “Evangelismos” General Hospital. Patients were initially considered as candidates for entrance into the study if they had a diagnosis of acute colonic pseudoobstruction, with a caecal diameter ≥10 cm on abdominal radiographs that failed to improve within 24 hours of conservative management. The
conservative treatment included administering nothing by mouth, nasogastric suction, intravenous fluid and electrolyte replacement and discontinuation (when possible) of any drugs that could adversely affect colonic motility such as narcotics and anticholinergic agents.

Acute colonic pseudoobstruction was defined as marked colonic distention without mechanical obstruction. Mechanical obstruction was ruled out by the finding of air throughout the colonic segments including the rectosigmoid on plain abdominal radiographs and abdominal CT scans. When air was not demonstrable in the left colon, mechanical obstruction was ruled out by radiographic contrast enemas.

Resolution of the syndrome was defined as a $\geq 10\%$ reduction of abdominal distention with a $\geq 20\%$ concomitant reduction of caecal diameter on abdominal radiographs, within 3 hours after neostigmine administration or immediately after colonoscopic decompression.

Relapse (treatment’s failure) was defined as a caecal diameter $\geq 8$ cm with a concommitant $\geq 10\%$ increase on abdominal radiographs with respect to the value that each patient had after initial resolution of the syndrome.

Exclusion criteria included failure to induce a resolution in colonic dilation after neostigmine administration or endoscopic decompression, signs of bowel perforation with peritoneal signs on physical examination or free air on radiographs or abdominal CT scans, a history of colon cancer or partial colonic resection, pregnancy or lactation.

The study protocol was approved by the local Ethical committees and written informed consent forms were obtained from all subjects before their entrance into the study.

**Neostigmine administration and endoscopic decompression**

All patients who failed to improve within 24 hours of conservative therapy received neostigmine 2 mg intravenously over a period of 3 to 5 minutes unless they had; a baseline heart rate <60 beats per minute, a systolic blood pressure <90 mmHg, active bronchospasm requiring medication, serum creatinine concentration of more than 3 mg/dl (265 µmol/lt). All patients were monitored by electrocardiography, atropine was available at the bedside and 1 mg was given intravenously as needed for symptomatic bradycardia. Patients were advised to remain supine for at least 60 minutes after the injection. Vital signs were recorded immediately before the injection, every five minutes for half an hour after the injection and every three hours afterward. The maximal abdominal circumference and the diameter of the caecum, ascending and transverse colon on plain abdominal radiographs were measured before and 3 hours after the injection.

All the patients who failed to respond within 3 hours after neostigmine administration or had any of the previously mentioned contraindications underwent colonoscopic decompression with tube placement over a guidewire, under fluoroscopic control. The procedure was considered successful if the ascending colon was reached and the tube was placed in the ascending colon or caecum (11). After the endoscopy the decompression tubes were placed on low intermittent suction and flushed with 20 to 30 ml of normal saline solution every 2 to 4 hours to maintain patency. All the endoscopies were performed by the same endoscopist (S.S.). The maximal abdominal circumference and the diameter of the caecum, ascending and transverse colon on plain abdominal radiographs were measured before and immediately after the colonoscopy.

**Randomization**

After initial resolution of colonic dilation, according to the previously described criteria, all patients were blindly randomized, using the closed envelope draw method, to receive daily either 29.5 gr of PEG (sach Klean-Prep, Pirex LTD, Norgin, Ireland) in 500 ml water, in two doses, or similar placebo. The placebo consisted of flour, sugar and vanilla powder,
manufactured by the Greek Naval Pharmacy whilst each preparation was provided in identical sachets. The administration was per mouth or via nasogastric tube. The patients immediately after initial resolution and for a 7-day period, were daily monitored for stool and flatus evacuations, maximal abdominal circumference and the diameter of the caecum, ascending and transverse colon on plain abdominal radiographs. The administration of the test solutions and the assessment of the patients’s symptoms and x-rays were performed in a blinded fashion.

In patients who had a relapse, treatment failure was established and neostigmine was administered as previously described. If the patient had failed to improve after neostigmine administration, an endoscopic decompression would have been performed. After the resolution of colonic dilation, these patients were eligible to receive open-label PEG.

Definitions of end-points
The primary end-point of the study was the relapse rate of acute colonic pseudoobstruction after initial resolution with neostigmine or endoscopic decompression.

Secondary end-points were i) the efficacy and safety of neostigmine administration in patients with acute colonic pseudoobstruction, ii) the feasibility, safety and efficacy of colonoscopic decompression with tube placement, in patients with acute colonic pseudo-obstruction, not responding to neostigmine administration, iii) the safety of PEG administration, in patients with acute colonic pseudo-obstruction, after the resolution of colonic dilation.

All adverse events were coded according to the World Health Organisation dictionary. For each adverse event, the causal relationship with the study drug and the event’s severity was noted.

Statistical analysis
The sample size calculation was based in a previous report (10) showing that the incidence of recurrent colonic dilation after neostigmine administration is approximately 40%. Assuming that the risk would be reduced to 10% by the administration of a PEG-based laxative, approximately 30 patients would be required for each group with a 2-tailed test to achieve a $\beta$ value of 0.2 and an $\alpha$ error of 5%. An interim analysis was decided to be done after the recruitment of 50% of patients.

Quantitative variables are expressed as mean±SE and qualitative variables as number and percent. Each continuous parameter between the two treatment groups was analyzed with two sample Student’s t-test. Categorical data were examined using the Chi-square test with Yate’s correction or Fisher’s exact test as appropriate. A $p \leq 0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS 10.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS
Primary end-point
During the study period 32 consecutive patients presented with Ogilvie’s syndrome. In 2 patients neostigmine administration and endoscopic decompression failed to induce a resolution in colonic dilation and as per protocol were excluded. These patients were found at laparotomy to have ischemic colonic necrosis that required bowel resection.

The remaining 30 patients were equally randomised in the two groups. Fourteen patients (47%) had a recent surgery (3 total hip replacement, 3 total knee replacement, 3 prostatectomy,
2 hysterectomy, 1 amputation of a leg, 1 lumbar laminectomy, 1 femoral fracture with internal fixation) whilst the rest had Parkinson’s disease (3 patients), previous cerebrovascular accident (3 patients), multiple sclerosis (2 patients), previous spinal cord injury with paralysis (2 patients), acute respiratory failure in two patients with chronic obstructive pulmonary disease and respiratory infection, myocardial infarction (1 patient), Alzheimer’s disease (1 patient), acute pancreatitis (1 patient), metastatic lung cancer (1 patient), Characteristics of patients at diagnosis are presented in table 1. The two groups were similar with regard to age, sex, history of constipation (defined as less than three evacuations per week during the last 6 months), previous use of narcotics and anticholinergics medications or laxatives, mechanical ventilation, history of recent surgical procedures, white blood cells count, abdominal circumference, colonic diameters on plain abdominal radiographs and type of initial therapeutic intervention.

<table>
<thead>
<tr>
<th>characteristic</th>
<th>PEG (n=15)</th>
<th>placebo (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (M/F)</td>
<td>8/7</td>
<td>8/7</td>
<td>0.99</td>
</tr>
<tr>
<td>age (years)</td>
<td>75.8±2.0</td>
<td>77.5±2.4</td>
<td>0.59</td>
</tr>
<tr>
<td>neostigmine (n)</td>
<td>12</td>
<td>13</td>
<td>0.99</td>
</tr>
<tr>
<td>endoscopic decompression (n)</td>
<td>5</td>
<td>3</td>
<td>0.68</td>
</tr>
<tr>
<td>mechanical ventilation (n)</td>
<td>2</td>
<td>3</td>
<td>0.99</td>
</tr>
<tr>
<td>narcotics, anticholinergics (n)</td>
<td>10</td>
<td>11</td>
<td>0.99</td>
</tr>
<tr>
<td>recent surgery (n)</td>
<td>8</td>
<td>6</td>
<td>0.71</td>
</tr>
<tr>
<td>history of constipation (n)</td>
<td>4</td>
<td>3</td>
<td>0.99</td>
</tr>
<tr>
<td>previous use of laxatives (n)</td>
<td>10</td>
<td>12</td>
<td>0.68</td>
</tr>
<tr>
<td>caecal diameter (cm)</td>
<td>12.5±0.4</td>
<td>13.3±0.3</td>
<td>0.18</td>
</tr>
<tr>
<td>ascending colon diameter (cm)</td>
<td>9.8±0.4</td>
<td>10.4±0.3</td>
<td>0.29</td>
</tr>
<tr>
<td>transverse colon diameter (cm)</td>
<td>8.5±0.3</td>
<td>9.0±0.2</td>
<td>0.25</td>
</tr>
<tr>
<td>abdominal circumference (cm)</td>
<td>115.5±2.3</td>
<td>116.6±2.2</td>
<td>0.73</td>
</tr>
<tr>
<td>white blood cells (x 10^9/mm^3)</td>
<td>17.1±0.7</td>
<td>16.2±0.8</td>
<td>0.45</td>
</tr>
<tr>
<td>contrast enema (n)</td>
<td>5</td>
<td>6</td>
<td>0.99</td>
</tr>
</tbody>
</table>

The two groups were also comparable after initial therapeutic intervention in terms of abdominal circumference and colonic diameters on plain abdominal radiographs (table 2).

<table>
<thead>
<tr>
<th>characteristic</th>
<th>PEG</th>
<th>placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>caecal diameter (cm)</td>
<td>6.8±0.6</td>
<td>7.1±0.6</td>
<td>0.75</td>
</tr>
<tr>
<td>ascending colon diameter (cm)</td>
<td>5.6±0.4</td>
<td>5.8±0.5</td>
<td>0.78</td>
</tr>
<tr>
<td>transverse colon diameter (cm)</td>
<td>5.1±0.4</td>
<td>5.0±0.4</td>
<td>0.89</td>
</tr>
<tr>
<td>abdominal circumference (cm)</td>
<td>99.8±1.8</td>
<td>100.8±1.4</td>
<td>0.69</td>
</tr>
<tr>
<td>neostigmine non-responders (n)</td>
<td>3</td>
<td>2</td>
<td>0.99</td>
</tr>
<tr>
<td>atropine (n)</td>
<td>1</td>
<td>1</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Characteristics of patients at the end of the treatment period (7 days after randomisation) are presented in table 3. Therapy with PEG resulted in a significant increase in stool and flatus evacuations (p=0.001 and 0.032 respectively) as well as in a significant decrease in the diameter of caecum, ascending and transverse colon and abdominal circumference (p= 0.017, 0.018, 0.014 and 0.008 respectively). During the follow-up period 5 (33.3%) patients from the placebo group, initially treated with neostigmine, relapsed as compared to none of the patients in the PEG group (p=0.04). The mean (SE) caecal diameter upon recurrence was 10 (0.7) cm (range 9-11 cm) whilst the mean (SE) time till the establishment of recurrent colonic dilation was 1.8 (0.8) days.

TABLE 3: Characteristics of patients at the end of the treatment period. Values are expressed as mean values ± SE.

<table>
<thead>
<tr>
<th>characteristic</th>
<th>PEG</th>
<th>placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>caecal diameter (cm)</td>
<td>3.4±0.2</td>
<td>5.6±0.8</td>
<td>0.017</td>
</tr>
<tr>
<td>ascending colon diameter (cm)</td>
<td>3.1±0.1</td>
<td>4.6±0.5</td>
<td>0.018</td>
</tr>
<tr>
<td>transverse colon diameter (cm)</td>
<td>3.0±0.06</td>
<td>4.2±0.4</td>
<td>0.014</td>
</tr>
<tr>
<td>abdominal circumference (cm)</td>
<td>92.2±1.1</td>
<td>101.3±2.9</td>
<td>0.008</td>
</tr>
<tr>
<td>stool evacuations (n/day)</td>
<td>1.4±0.1</td>
<td>0.6±0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>flatus evacuations (n/day)</td>
<td>2.4±0.1</td>
<td>1.5±0.3</td>
<td>0.032</td>
</tr>
<tr>
<td>relapse (n)</td>
<td>0</td>
<td>5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

All 5 patients with recurrent colonic dilation received neostigmine. It was successful in 2 cases (2/5, 40%) whilst 3 patients had an endoscopic decompression. All 5 patients, after the resolution of colonic dilation, received PEG in the open-label arm of the study. There were no further recurrences after 7 days of treatment.

Secondary end-points

Neostigmine was administered in 25 patients at presentation and in 5 patients upon recurrence of colonic dilation. It resulted in resolution of colonic dilation in 22 (88%) and 2 (40%) of cases respectively (figure 1). The most frequent adverse effect was cramping abdominal pain which was noted by 17 (56.6%) patients. It was described as mild by 6 (20%) patients and as moderate to severe by 11 (36.6%) patients. Four (13.3%) patients vomited and 10 (33.3%) experienced excessive salivation. Two patients developed symptomatic bradycardia and atropine was administered as per protocol.

An urgent endoscopic decompression was performed in 8 patients at presentation (5 from PEG group and 3 from the placebo group). These patients were non-responders to neostigmine (n=3) or had a contraindication for neostigmine administration (n=5). It was successful and uneventful in all cases. Three patients also had a successful and uneventful colonoscopic decompression upon recurrence of colonic dilation due to non-response to neostigmine. Colonic dilation did not recur in any of the patients who had endoscopic decompression.

Therapy with PEG did not result in any serious adverse event and none patient stopped therapy. Four patients from the PEG group and 1 patient from the placebo group developed nausea and 1 patient from the PEG group vomited after a single dose. 3 patients from the PEG group developed mild abdominal colicky pain as compared to 1 patient from the placebo group.
DISCUSSION

Acute colonic pseudoobstruction is a common clinical scenario for which gastroenterologists are consulted. During the last decade the management options have changed, especially with the advent of neostigmine. Currently, it is generally accepted that neostigmine induces an initial response rate in approximately 90% of cases (9,10). However, the rates of sustained response appear to be significantly lower. The only prospective, placebo-controlled clinical trial thus far (9), reports a sustained response rate of 89%, whilst Loftus et al (10), in a retrospective analysis of 18 patients, suggest that the sustained response rate might be as low as 61%. Patients who present with recurrent colonic dilation after neostigmine administration, a second trial of the drug is indicated (9). In non-responders to neostigmine, urgent colonoscopic decompression with a tube placement in the ascending colon or distally is indicated (8,11).

The present trial is the largest prospective study in patients with acute colonic pseudoobstruction reported, so far. In our series neostigmine resulted in an initial response in up to 88% of cases within 3 hours of administration. The three-hour period was chosen because of the short half-life of neostigmine. Our results confirm previous studies showing that approximately 90% of patients initially respond to neostigmine (9,16,17). However, the rate of sustained response to neostigmine appears significantly lower. Five out of the 13 patients (38.9%) who were initially randomised in the placebo group and received neostigmine as first-line therapy, had recurrent colonic dilation within 7 days after drug administration. A second trial of neostigmine was attempted, but its efficacy was far lower (40%). The seven-day period was chosen because patients usually have recurrent colonic dilation within the first four days after initial therapeutic intervention (11).

To our knowledge this is the first trial showing that the daily administration of polyethylene-glycol electrolyte balanced solution in patients with acute colonic pseudoobstruction after initial successful therapeutic intervention, might increase the sustained response rate. There were three kinds of evidence that led us to investigate a possible therapeutic role of PEG in patients with acute colonic pseudoobstruction. First, polyethylene-glycol based laxatives induce an acceleration in colonic transit predominantly through the distal colon (18,19) which is principally affected in Ogilvie’s syndrome. This effect is attributed either to an increased faecal bulk in the distal colon that triggers myogenic peristalsis, or to a direct effect on colonic motility (20), although the latter has not been demonstrated unanimously (21). Additionally, previous studies (22,23) indicate that the volatile, short-lived gas nitric oxide (NO), one of the major inhibitory neurotransmitters released by enteric neurones may by responsible for gut dysmotility and dilation. In vitro (1) and in vivo (24) addition of the NO synthase inhibitor nitro-L-arginine methyl ester (L-NAME) was followed by strong phasic contractions in colonic muscular circular strips of a patient with megacolon and resolution of dilation respectively. Recent evidence suggests that polyethylene glycol might reduce the rate of NO production acting either as a storage molecule (25) or by decreasing NO synthase (26).

We decided to adopt a strict and well-standardised protocol for the evaluation and follow-up of patients with acute colonic pseudoobstruction. Initial response to neostigmine was defined as a ≥10% reduction of abdominal distention with a ≥20% concomitant reduction of caecal diameter on abdominal radiographs, within 3 hours after neostigmine administration. These values were based on the previously published results by Ponec et al (9). All “responders” according to the previously described criteria also had prompt evacuation of flatus or stool within three hours after neostigmine administration. During follow-up, for ethical reasons, we arbitrarily defined the relapse as a caecal diameter ≥8 cm with a concomitant ≥10% increase on abdominal radiographs with respect to the value that each patient had after initial resolution of the syndrome. The mean (SE) caecal diameter upon recurrence was
10 (0.7) cm (range 9-11 cm) and this proves that all patients had clinically significant colonic dilation upon recurrence.

Our results should be interpreted with some caution because we did not enroll the desired number of patients and thus a type I error can not be excluded. However, in the largest prospective study in patients with acute colonic pseudoobstruction reported so far, we found a clear superiority of PEG over placebo and we think that it would be inappropriate to deprive other patients of such an effective therapy.

In conclusion our study confirms previously published studies showing that patients with acute colonic pseudoobstruction usually have an increased initial response rate to neostigmine administration. However, the sustained response rate appears significantly lower. The administration of polyethylene glycol electrolyte balanced solution after the resolution of colonic dilation increases the sustained response rate after initial therapeutic intervention.

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During the preparation of the manuscript Professor A. Avgerinos passed away. We would like to express our gratitude for being a great teacher and mentor to many young gastroenterologists.

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CONFLICT OF INTEREST STATEMENT:
Nothing to declare.
REFERENCES


Legend for figure 1. Abdominal radiographs in a patient with acute colonic pseudoobstruction A) before and, B) three hours after neostigmine administration.
Figure 1a
Figure 1b.
The effect of polyethylene glycol electrolyte balanced solution on patients with acute colonic pseudoobstruction after the resolution of colonic dilation: a prospective, randomised, placebo-controlled trial

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