Intravenous glucagon beneficial during colonoscopy in patient with IBS

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ABSTRACT

Background and Aim: Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort and altered bowel habits. Patients with IBS requiring colonoscopy take longer time to cecum with higher need for medications used for conscious sedation. Glucagon is routinely used during endoscopic procedures to reduce peristalsis that interfere with the procedure. However, randomized controlled data using glucagon during endoscopic procedures are lacking. We designed a prospective randomized placebo-controlled trial to study the effect of intravenous glucagon given during colonoscopy. Materials and Methods: We received approval from the FDA for this off-label use of glucagon during colonoscopy. This is a double-blind randomized placebo-controlled study. Patients were selected based on ROME III criteria for IBS; patients who met Rome III criteria and had an indication for colonoscopy for age-specific colon cancer screening or for work up of any alarm signs. We selected 34 patients meeting the Rome III for IBS and randomized into Group A and Group B. Both the performing endoscopist and patients were blinded. These patients in both groups initially received a standard dose of conscious sedation, up to 100 mcg of fentanyl and up to 5 mg of midazolam intravenously. In Group A, 17 patients, in addition to conscious sedation, received 1 ml saline as placebo. In Group B, 17 patients, in addition to conscious sedation, received 1 mg of intravenous glucagon. Parameters evaluated were as follows: 1) Total time required for colonoscopy 2) Completion of colonoscopy as documented by cecal intubation or visualization of appendicular orifice 3) Level of comfort in patient concerned to post-procedure spasmodic pain, which was based on Wong-Baker FACES pain rating scale and 4) Calculate the amount of sedation required in both groups of patients and also at what extent glucagon helped to decrease the requirement of sedatives. Data was analyzed using the student t-test.

Keywords: Colonoscopy, Glucagon, IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort and altered bowel habits. Altered gastrointestinal (GI) motility, visceral hyperalgesia, disturbance of brain–gut interaction, abnormal central processing, autonomic and hormonal events, genetic and environmental factors, and psychosocial disturbances are variably involved, depending on the individual. Therefore for patients with IBS, we used glucagon as an antispasmodic agent to expedite the colonoscopy with less pain and to achieve completeness of colonoscopy. IBS-associated pain is believed to result in part from disordered smooth muscle activity coupled with sensory dysregulation resulting in visceral hypersensitivity. Endocrine pathways that modulate gastrointestinal motility represent novel therapeutic targets in IBS and other gastrointestinal disorders. Glucagon or glucagon-like peptide-1 (GLP-1) is normally released after food intake and stimulates insulin release and reduces
gastric emptying and intestinal motility. In humans, GLP-1 inhibits intestinal motility in healthy subjects and patients with IBS.\textsuperscript{[2,3]} Patients with IBS requiring colonoscopy take longer time to cecum with higher need for medications used for conscious sedation.\textsuperscript{[4,5]} Glucagon is routinely used during endoscopic procedures to reduce peristalsis that interfere with the procedure. Glucagon is released after food intake to act as an incretin. Glucagon also inhibits gastric emptying and increases satiety. It was seen in some study that glucagon in rats inhibits small bowel motility.\textsuperscript{[2]} Glucagon inhibits both electrical and pressure rhythms in all subjects. Evidence is produced to suggest a direct action on colonic smooth muscle. A controlled trial using glucagon during routine barium enema examinations suggest that it may prove to be useful for hypotonic examinations of the colon where painful spasm is present.\textsuperscript{[3]} A literature review which showed that 2 milligrams of glucagon given intramuscularly was found to be safe and effective in overcoming functional spasm, permitting more detailed evaluation of organic narrowing. The relatively infrequent side effects and few contraindications seen with glucagon make it the drug of choice when reduction in intestinal tone is indicated.\textsuperscript{[4]} It has been well established that IBS is major factor in making colonoscopy technically difficult.\textsuperscript{[7,8]} Our aim was to study the effects of glucagon on gastrointestinal motility patients with irritable bowel syndrome (IBS), specifically its possible role in expediting colonoscopy with improved tolerance and to achieve completeness of colonoscopy.

**STUDY DESIGN AND METHOD**

We designed a prospective randomized placebo controlled study to look for the effect of intravenous glucagon given during colonoscopy. We used 1 mg of glucagon in addition to sedative medications, fentanyl and midazolam, to evaluate the completeness of colonoscopy and post-procedure comfort in patient with IBS. We have screened 64 patients and selected 34 patients based on Rome III criteria for IBS who presents for colonoscopy either for age-appropriate screening or for alarm symptoms such as weight loss or blood in the stool.

**Study period was 11 months and followings were the criteria**

**Inclusion Criteria:** Patients ages were above 18 yrs and also there was no restriction on race, and both gender were included for meeting the Rome III inclusion criteria.

**Exclusion criteria for subjects:** Patients with known diabetes, pheochromocytoma, allergic to glucagon, insulinoma as well as those who does not meet Rome III diagnostic criteria.

The Rome III Diagnostic Criteria*: (A system for diagnosing functional gastrointestinal disorders based on symptoms) for IBS is as follows:

<table>
<thead>
<tr>
<th>Rome III diagnostic criteria * for irritable bowel syndrome</th>
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<tr>
<td>Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following</td>
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<tr>
<td>(1) Improvement with defecation</td>
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<tr>
<td>(2) Onset associated with a change in frequency of stool</td>
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<tr>
<td>(3) Onset associated with a change in form (appearance) of stool</td>
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</table>

Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. • Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation for subject eligibility.


We have screened 64 patients, and 34 patients meeting the criteria were randomized into two groups comprising of 17 patients each.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tr>
<td>• IBS (using ROME III criteria as mentioned in above table)</td>
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<tr>
<td>• Undergoing screening or diagnostic colonoscopy</td>
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<tr>
<td>• Known allergy to glucagon</td>
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<tr>
<td>• Previous diagnosis or ongoing workup for pheochromocytoma, insulinoma diabetes</td>
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</tr>
</tbody>
</table>

Out of two groups, one group received the study medication and the other group received placebo. All patients initially received a standard dose of conscious sedation, up to 100 mcg of fentanyl and up to 5mg of midazolam intravenously. In Group A, patients received 1 ml saline as placebo and in Group B, patients received 1 mg of IV glucagon. Both the performing endoscopist and patients were blinded. Procedures were performed by a
second or third year fellows under the supervision of an attending physician.

Parameters evaluated were as follows:

- Time to cecal intubation
- Completion of colonoscopy as documented by cecal intubation and examining the colon on return
- Level of comfort in patients in regards to post-procedure pain, which was based on the Wong-Baker FACES pain rating scale
- Total amount of sedation required

Any diagnostic or therapeutic procedures were done upon return from cecum to minimize variability. There was no adverse event noted post procedure.

RESULTS

Statistical analysis

Sixty four patients were screened at two clinical sites and selected 34 patients were randomized and received study trial. Demographic data of patient participation in the study is shown in Table 1. All the patients who met the criteria participated in study successfully. Patient characteristics are shown in Table 1. Mean age was 55 years, >65% of patients were women and almost nearly equal 40–50% of patient were Hispanic and African American. After gathering all the data, it was analyzed using student t-test. As mentioned in Table 1 demographics, the average age of the patient is about 55 years and number of male patient > female patient.

The study showed a statistically significant (P value <0.019) shorter time to intubate the cecum patients receiving glucagon as 7.5+/−3.2 minutes compared to patients who did not receive glucagon as 10.9+/−4.8 minutes [Figures 1 and 2].

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data</th>
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<td><strong>Demographics</strong></td>
<td><strong>Group A NO Glucagon</strong></td>
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<tr>
<td>Average age</td>
<td>55.35 ± 4</td>
</tr>
<tr>
<td>Male</td>
<td>6 (35.29%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (64.71%)</td>
</tr>
<tr>
<td>Race</td>
<td>7 Hispanic (41.71%)</td>
</tr>
<tr>
<td></td>
<td>10 African American (58.29%)</td>
</tr>
<tr>
<td></td>
<td>2 Caucasian (11.77%)</td>
</tr>
<tr>
<td>Indication</td>
<td>4 surveillance</td>
</tr>
<tr>
<td></td>
<td>5 screening</td>
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<td></td>
<td>8 diagnostic</td>
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</table>

Figure 1. The average time to cecum was 7.5+/−3.2 minutes in patients who received glucagon and those patients who did not receive the glucagon the time to cecum was 10.9+/−4.8 minutes.

Figure 2. The average time to complete colonoscopy was 14.8+/−6.3 minutes in patients who received glucagon and those patients who did not receive the glucagon the time to complete colonoscopy 17.4+/−3.7 minutes.

The other parameters studied did not show statistical significance between the two groups which includes:

- Total time for completion of colonoscopy
- Level of comfort in patients in regards to post-procedure pain
- Total amount of sedation required

No adverse effects were noted from the intravenous use of glucagon during colonoscopy.

DISCUSSION

Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal tract. The diagnosis should be made on clinical grounds, using symptom-based criteria such as the Rome III criteria. The exact cause of IBS remains obscure, and there are no structural or biochemical abnormalities demonstrated in the gut to explain the symptoms experienced by sufferers. However, proposed causes include abnormalities of muscle and nerve function, increased or reduced gastrointestinal transit, reduced tolerance to painful stimuli, and alterations in gut bacteria (Cann et al., 1983; Kassinen et al., 2007; Moriarty and Dawson 1982; Trimble et al., 1995).
Since IBS is such a common disease, which is seen in 50% of cases in GI practice, colonoscopy being performed on these patients can be sometimes challenging. Thus it takes longer time to do colonoscopy. Several studies have shown that it take much longer time in routine/diagnostic colonoscopy in IBS patients. These studies did not show the glucagon use in colonoscopy is beneficial because the patient population is not selected for IBS. It has been well established that IBS is a major factor in making colonoscopy technically difficult. So how do we reduce the colonoscopy time? To answer this question, our study has shown that glucagon use in colonoscopy reduces cecal intubation time; glucagon and glucagon-like peptide (GLP-1), which is released after food intake to act as an incretin. These incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), work together to reduce postprandial hyperglycemia by glucose-dependent insulin secretion and inhibition of glucagon release, as well as inhibition of GI motility and gastric emptying. GLP-1 is considered the more effective of the two incretins due to its additional inhibitory effects on GI motility.

Glucagon also inhibits gastric emptying and increases satiety. Our aim was to study the effects of glucagon on gastrointestinal motility patients with irritable bowel syndrome (IBS). Glucagon has been used in ERCP and upper endoscopy routinely to slow down the gut motility and facilitate the procedure. It has been seen that glucagon causes inhibitory effect on MMC (migrating motor complex) and it also inhibits transit of intestine. It reduces contraction frequency by directly acting on smooth muscle of intestines. Therefore, we hypothesized that decreasing GI contractility via glucagon would null the inherent motility disturbances in patients with IBS.

In our study, we used glucagon as direct smooth muscle relaxant by using intravenous during colonoscopy in IBS patient. Patient who received glucagon during colonoscopy has less cecal intubation time as compared to the patient who did not receive the glucagon. As we have mentioned earlier there was no change in rest of parameter.

The limitation of our study was that our study was small pilot study. It may need study with large sample to have better perspective of the results on other parameter of study.

In summary, patients with IBS as determined by the Rome III criteria going for routine colonoscopy may benefit from intravenous glucagon administered during the procedure to reduce the time for cecal intubation. Use of glucagon during colonoscopy was well tolerated by the patients.

Conflict of interest statement: There is no Conflict of Interest of any of the authors.

Source of support: None

REFERENCES