Oral Vancomycin as an Adjuvant Treatment in IBD

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Objective: To study the efficacy of oral vancomycin (POV) treatment in pediatric inflammatory bowel disease (IBD).

Methods: We conducted retrospective and prospective chart reviews, identifying patients using the Division’s Inflammatory Bowel Disease (IBD) registry, ICD-9 and ICD-10 codes for IBD, and recall of patients receiving POV. Patients aged 2–21 years with active IBD at initiation of POV were included unless they had Clostridium difficile infection or primary sclerosing cholangitis (PSC). Pre- and posttreatment analysis included a Physician Global Assessment (PGA), pediatric ulcerative colitis (UC) activity index (PUCAI), and an abbreviated pediatric Crohn’s disease (CD) activity index (PCDAI). The Wilcoxon Signed Ranks test, determined if pre- and post-POV rankings of symptom severity differed. Mann-Whitney U tests assessed improvement in presenting symptoms.

Results: Nineteen patients met inclusion criteria (12 CD and 7 UC). POV improved the PGA score in 16 of 19 patients ($P < 0.001$). Mean PGA score pretreatment was $3 ± 0.471$; posttreatment mean of $1.58 ± 0.769$. Abdominal pain ($P < 0.001$), diarrhea ($P < 0.002$), and blood in stool ($P < 0.001$) showed significant improvement. PUCAI and PCDAI scores, pretreatment means of $50 ± 17$ and $33 ± 9$, respectively, also improved with mean score reduction of $23$ in CD and $38$ in UC patients after POV initiation ($P$-value $< 0.0001$). This improvement was noted for both IBD subtypes.

Conclusions: POV may be an effective adjuvant treatment for pediatric IBD. Its effectiveness is likely due to a combination of its anti-tumor necrosis factor alpha-activity and its influence on the gut microbiome. Further controlled studies of POV in IBD are warranted to determine the most efficacious use of POV in pediatric IBD.

Aim: This study attempts to expand on the current literature to determine efficacy of POV as an adjuvant therapy in treating active IBD in children.

Key Words: pediatric IBD, Crohn’s disease, ulcerative colitis, vancomycin, microbiome

INTRODUCTION

The incidence of pediatric patients with inflammatory bowel disease (IBD) continues to increase significantly with 5–11 cases per 100,000 children across the United States and Canada.1,2 Antibiotics have been proven useful in the treatment of IBD. However, these traditional antibiotics are systemically absorbed, and have significant side effects.3,4

Vancomycin is a glycopeptide antibiotic first used commercially in the 1950s, and has been a mainstay of treatment for serious bacterial infections involving gram-positive species. It works by inhibiting cell wall synthesis. For the gastroenterologist, oral vancomycin (POV) has been an important medication in the treatment of IBD flares associated with Clostridium difficile, as well as dysbiosis.5,6 It is believed to have a better side effect profile compared to traditional IBD antibiotics, and does not increase the risk for vancomycin resistant enterococcus.7,9

Early studies, including one by Dickensen et al, were able to show improvement with POV in acute colitis flares when used in short, week-long bursts, leading to a reduction in surgical interventions.10 These early studies attributed this effect to the alteration of the patients’ microbiomes, but more recent studies have shown its effect to be at a molecular level.11 In vitro studies suggested that vancomycin downregulates tumor necrosis factor alpha (TNF-α), a cytokine involved in systemic inflammation. This results in a dose dependent decrease in its downstream effects on pro-inflammatory proteins within the cells, specifically in monocytes that play a key role in adaptive immunity.12,13 Indeed, among the most effective current treatment options for IBD are the anti-TNF-α biologic drugs, such

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as infliximab and adalimumab. In vivo studies done in patients with IBD with concurrent primary sclerosing cholangitis (PSC) show how POV also acts on regulatory T cells. As such, POV may prove just as beneficial in the treatment of IBD.

As with antibiotic use, the possible side effects of vancomycin are concerns. Even though it is widely accepted that POV is not absorbed systemically, some case reports demonstrate systemic absorption when gastroenterology mucosal integrity is lost, such as during active infections. Concerns for the formation of resistant bacteria, such as C. difficile remain relevant. Additionally, literature has also associated POV to cause alteration of bile acid metabolism and decrease insulin sensitivity. All of these possible side effects must be taken into consideration when using POV.

To date, no studies report the outcome of IBD patients treated with POV in absence of PSC or an active C. difficile infection. POV may be a viable treatment option for IBD, both in short and long term. If POV proves to be useful, future studies to assess the cost-effectiveness and side effect profile of POV versus other IBD therapies will be helpful. Should POV be shown to be an effective treatment in pediatric IBD, we will be able to add another medicine to the medical arsenal to treat IBD, particularly as patients are at risk for developing antibodies to biologics and efficacy of that treatment could wane over time.

METHODS

The study was a retrospective chart review with a prospective arm. The study inclusion criteria consisted of all patients with IBD, age 2–21 years old, treated in our practice during the period from January 1, 2008 through December 31, 2016. Patients with concurrent PSC and/or active C. difficile infection were excluded. Patients were identified using our pediatric IBD research registry, ICD-9 and ICD-10 codes, along with practitioners’ own recall. During the study period two patients beginning treatment with POV were also prospectively followed and included in the analysis.

Treatment intervention was defined as starting POV at any given point after diagnosis with IBD. Physician Global Assessment (PGA) scores were determined pre- and posttreatment by a combination of common patient symptoms to track clinical response as well as common laboratory markers including ESR, CRP, hematocrit, platelet count, and fecal calprotectin. PGA, abbreviated Pediatric Crohn’s Disease Activity Index (PCDAI), as well as the Pediatric Ulcerative Colitis Activity Index (PUCAI) were used to assess symptom improvement and disease activity. We further analyzed the presence of common symptoms both pre- and posttreatment to track clinical response. Patient records were reviewed for the presence or absence of the following common symptoms: abdominal pain, diarrhea, blood in stool, and anemia. Patients were also ranked based on the severity of symptoms using the PGA as follows: 1 = inactive, 2 = mild, 3 = moderate, 4 = severe.

Statistical Analysis

Mann–Whitney U tests were used to determine whether treatment changed the number of patients experiencing each symptom. Ranking data were analyzed using Wilcoxon Signed Ranks test to determine if pre- and post-POV intervention rankings of symptom severity significantly differed.

RESULTS

AS of 2016, 195 pediatric IBD patients were followed by our practice. Of these, 19 patients, or 10%, were eligible for this study. Subjects were evenly distributed among sex, but the large majority were >5 years old, Caucasian, and with a CD predominance (Table 1). We demonstrated that POV improved the PGA score in 16 of 19 patients (P < 0.001), with no patients worsening (Fig. 1). As seen in Figure 2, individual symptom reporting also demonstrated significant improvement (P < 0.002) demonstrating clinical response to treatment. Abbreviated PCDAI and PUCAI scores both improved, though no significant difference was noted between the two disease types (Fig. 3). In our study no patients were on monotherapy with POV. Nine patients (47%), five with CD and four with UC, had POVC alone added to their treatment regimen, with 89% of those showing disease improvement (Table 2). These patients showed a mean score reduction from 56 to 19 in the patients with UC and 36 to 12 in patients with CD. Ten patients (53%), seven with CD and three with UC, were started on other medications along with POV including, other antibiotics, 5ASA, immunomodulators, steroids, and biologics.

| Demographic Variable | Frequency (n) | % |
|----------------------|---------------|---|
| **Gender**           |               |   |
| Male                 | 9             | 47.4 |
| Female               | 10            | 52.6 |
| **Age (years)**      |               |   |
| <5                   | 2             | 10.5 |
| 5–10                 | 4             | 21.1 |
| 11–15                | 8             | 42.1 |
| 16–19                | 5             | 26.3 |
| **Race**             |               |   |
| African American     | 4             | 21.1 |
| Middle Eastern       | 1             | 5.3 |
| Caucasian            | 12            | 63  |
| Hispanic             | 1             | 5.3 |
| Biracial             | 1             | 5.3 |
| **Disease type**     |               |   |
| CD                   | 12            | 63  |
| UC                   | 7             | 37  |
DISCUSSION

As the incidence of pediatric IBD continues to rise, research into new treatments has become increasingly important. Antibiotics have historically been used in the treatment of IBD, and their efficacy is believed to be secondary to their alteration of the gut microbiome. However, some of these antibiotics have significant systematic side effects due to their gut absorption. Though POV has shown efficacy in patients with UC and PSC, its mechanism of action is hypothesized to be related to its effects on gram-positive organisms in the gut microbiome.

An alternative hypothesis suggests the mechanism is due to the downregulation of TNF-α cytokine secreted by monocytes. Previous studies have not investigated its effects on pediatric IBD patients without PSC and/or C. difficile infection.

Many studies have identified an altered microbiome with reduced diversity in patients with IBD. Microbial composition results of studies vary based on the methods of sampling, disease type and activity, and location of disease. Increases in gram-negative organisms, particularly adherent *Escherichia coli* have been associated with ileal CD. Patients with IBD repeatedly
have lower populations of Bacteroides and Lachnospiraceae than healthy controls. Mucosa-attached biofilms associated with *Bacteroides fragilis* have been associated with 90% of CD patients and 60% of UC patients. Some studies have hypothesized that overgrowth of *E. coli* occurs in the absence of competition from gram-positive bacteria. This mechanism would not be supported by our findings of improvement after treatment with POV since POV is broadly active only against gram-positive bacteria and our patients still showed improvement.

This study selected pediatric patients with IBD, without biliary disease or *C. difficile*, receiving POV as a part of their IBD therapy. We retrospectively reviewed their clinical records before and after initiation of POV treatment to form a PGA score and a disease activity score. We showed that most of our patients (84%) had improvement of their disease with POV treatment and that there was no statistical significance between the two subtypes of IBD. In a subgroup analysis, the patients who had only POV as the new addition to their treatment demonstrated improvement (Table 2).

Although a previous study of POV by Dickinson et al showed some promise in their patients avoiding surgical intervention, the study was unable to display statistical significance. Though our study was not a controlled study, our design was intentionally concentrated on our general IBD population and their clinical outcomes. We were able to demonstrate statistical significance in disease activity and symptom improvement. Prior pediatric studies by Cox et al and Davies et al were restricted to a specific subset of IBD patients, those with PSC. These studies also focused more on the tissue and molecular process of the disease and treatment.

Though our findings are promising for the use of POV, this study has several limitations. Sample size in this study is larger than previous pediatric POV studies, but was still limited. Relying in part on clinician recollection for enrollment can lead to a significant recall bias. The recall bias was limited by using the Division’s IBD Registry and reviewing all of our IBD patients’ office chart for vancomycin use. The study is also limited

| Patient # | Current Medications Before POV | Medications Added With POV |
|-----------|-------------------------------|---------------------------|
| 1         | Antibiotics, immunomodulator  | Biologic                  |
| 2         | 5ASA, antibiotic, probiotic   | Immunomodulator systemic steroids |
| 3         | 5ASA                          | None                      |
| 4         | 5ASA                          | 5ASA                      |
| 5         | 5ASA, immunomodulator, systemic steroids | None |
| 6         | Antibiotics, immunomodulator, biologic, systemic steroids | Antibiotic |
| 7         | 5ASA, immunomodulator         | Antibiotic, biologic, systemic steroids |
| 8         | 5ASA, antibiotic, immunomodulator | None |
| 9         | 5ASA                          | None                      |
| 10        | Immunomodulator, biologic, systemic steroids | None |
| 11        | 5ASA, immunomodulator, biologic, systemic steroids | None |
| 12        | 5ASA                          | None                      |
| 13        | 5ASA, nutrition therapy       | None                      |
| 14        | Antibiotic, immunomodulator   | 5ASA                      |
| 15        | Immunomodulator, systemic steroids | Antibiotic, topical steroids |
| 16        | Antibiotic, immunomodulator, systemic steroids | None |
| 17        | Antibiotics, immunomodulator, biologic | Systemic steroids |
| 18        | 5ASA, systemic steroids       | Probiotics                |
| 19        | 5ASA, immunomodulator         | Systemic steroids          |
by its lack of a control group. Unfortunately, with so many variables analyzed, finding a matched control for each patient was not seen as feasible. Nevertheless our results are promising for POV to be used as an adjuvant treatment in IBD and further prospective studies are warranted.

Follow-up studies could be designed as case-controlled or placebo-controlled trials using the addition of POV versus current standard of care. Furthermore, in such studies, not only can treatment efficacy be better determined, but patients could also be evaluated for alterations in the microbiome, metabolome and cytokine profile pre- and posttreatment to evaluate changes associated with response.

POV shows promise as an adjuvant IBD medication, though its role in the treatment algorithm is still unclear. Among antibiotics currently being used orally in IBD, POV has less systemic effects leading to a better side effect profile and therefore should be considered a frontline choice when considering antibiotic therapy in IBD.

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