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Original Article

Comparison of PUCAI Score in Mesalazine-Treated Children with Ulcerative Colitis

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Abstract:

Background: Ulcerative colitis is a chronic idiopathic inflammatory bowel disease (IBD) characterized by intestinal inflammation confined to the superficial mucosal layer. Mesalazine, a 5-aminosalicylic acid (5-aminosalicylic, or 5-ASA) compound, is most often used as first-line therapy for mild to moderate ulcerative colitis. *The* Pediatric Ulcerative Colitis Activity Index (PUCAI) is a non-invasive multi-item measure that has been shown to be valid, reliable, and responsive to short-term changes in several clinical trials and cohort studies. Therefore, this study aims to compare the PUCAI scores in children with ulcerative colitis who received mesalazine therapy to those who did not.

Methods: We performed a retrospective database analysis of 12 patients, who were diagnosed with ulcerative colitis at Dr. Kariadi General Hospital, Semarang, Indonesia in a span of 1 year. We included all cases of pediatric patients with ulcerative colitis, then we divided them into 2 groups, the group receiving mesalazine therapy and the group who did not. We monitored the development of PUCAI scores before and after treatment.

Results: The number of samples in this study was 12 samples. All sample data were taken based on data from pediatric gastroenterohepatology patients diagnosed with colitis ulcerative based on pathology anatomy results, who were treated in the pediatric ward of RSUP Dr. Kariadi Semarang. From the result of the paired t-test, there was a significant decrease in PUCAI score in patients who received Mesalazine, ($p = 0.007$), while those who did not receive mesalazine, did not show any significant decrease in PUCAI score.

Conclusion: Ulcerative colitis (UC) is a chronic relapsing inflammatory condition. UC is often treated with mesalazine as the first-line treatment. The use of the PUCAI score is an appropriate tool to determine the progression of this disease. Based on the data obtained, the administration of mesalazine therapy in children with ulcerative colitis can improve PUCAI scores compared to children who do not receive mesalazine therapy.

Keywords: mesalazine, ulcerative colitis, PUCAI score

Introduction

Ulcerative colitis is a chronic idiopathic inflammatory bowel disease (IBD) characterized by intestinal inflammation confined to the superficial mucosal layer. It may involve the rectum only, the distal colon, or the entire colon, usually contiguously. The classic symptoms of ulcerative colitis include bloody diarrhea, urgency, and tenesmus. Mesalazine, a 5-aminosalicylic acid (5-aminosalicylic, or 5-ASA) compound, is most often used as first-line therapy for mild to moderate ulcerative colitis. However, the precise mechanism of action of mesalazine is still poorly elucidated. It is believed to exert a negative effect on the cyclooxygenase and lipoxygenase pathways, thereby reducing the formation of pro-inflammatory prostaglandins and leukotrienes. Peroxisome proliferator-activated gamma-receptors are also involved in colonic inflammation and have been identified as targets of 5-ASA action. Furthermore, mesalazine may have antioxidant properties that reduce tissue injury and play a role in the inhibition of T cell activation and proliferation.[1,2]

Oral mesalazine compounds have been shown to be effective in inducing and maintaining remission in patients with ulcerative colitis. Mesalazine exerts a therapeutic effect through local topical activity on the inflamed mucosa. Oral mesalazine in its unchanged form is almost completely absorbed by the small intestine, with very little of the intact drug reaching the large intestine. Therefore, the main objective of the various formulations currently available in the market is to optimize drug delivery to the affected colon and minimize systemic absorption. This promotes maximum therapeutic efficacy at the lowest possible dose, which in turn reduces side effects.[3,4]

The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a non-invasive multi-item measure that has been shown to be valid, reliable, and responsive to short-term changes in several clinical trials and cohort studies. The PUCAI has been proven to have excellent correlation with the invasive Mayo score, physician global assessment, and colonoscopy appearance.[5,6] Therefore, this study aims to compare the PUCAI scores in children with ulcerative colitis who received mesalazine therapy to those who did not.

Methods

We performed a retrospective database analysis of 12 patients, who were diagnosed with ulcerative colitis at Dr. Kariadi General Hospital, Semarang, Indonesia in a span of 1 year. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical Committee. We included all cases of pediatric patients with ulcerative colitis, then we divided them into 2 groups, the group receiving mesalazine therapy and the group who did not. We monitored the

development of PUCAI scores before and after treatment. Statistical data was collected and analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Co.). Shapiro-Wilk analysis was used to determine the normality of the data and continued with a paired t-test to compare PUCAI scores before and after therapy. The data is significant if $p < 0.05$.

Results

The number of samples in this study was 12 samples. All sample data were taken based on data from pediatric gastroenterohepatology patients diagnosed with colitis ulcerative based on pathology anatomy results, who were treated in the pediatric ward of RSUP Dr. Kariadi Semarang. Characteristics of the data are in the table below (**Table 1**).

Table 1. Baseline characteristics of children with ulcerative colitis

Characteristics	Frequency
Gender, n (%)	
Boys	7 (41.7)
Girls	5 (58.3)
Age (years) *	7.2±3.9
Pre-treatment PUCAI score*	40.8±18.5
Post-treatment PUCAI score*	5.0±9.2
Length of treatment (days) *	180.0±33.8
Mesalazine therapy, n (%)	
Yes	9 (75)
No	3 (25)

***Data presented in Mean±Standard Deviation. PUCAI: Pediatric Ulcerative Colitis Activity Index.**

Based on the baseline characteristics data, our patients were predominantly boys (41.7%), with mean age of 7.2±3.9 years. The mean pre- and post- treatment PUCAI score were 40.8±18.5 and 5.0±9.2. Nine patients (75%) received mesalazine therapy while the other 3 patients did not. The mean duration of treatment was 180.0±33.8 days.

Shapiro-Wilk analysis was not significant ($p>0.05$) for pre-and post-treatment PUCAI score in both groups, indicating a normal distribution of those data. We then continued with paired-t test to evaluate the changes of PUCAI score pre-and post-treatment in both mesalazine and non-mesalazine group. (**Table 2**)

Table 2. Data normality test

Treatment		p
Pre	Mesalazine	0.85
	Non- mesalazine	1.000
Post	Mesalazine	0.97
	Non- mesalazine	1.000

From the result of the paired t-test, there was a significant decrease in PUCAI score in patients who received Mesalazine, (p = 0.007), while those who did not receive mesalazine, did not show any significant decrease in PUCAI score.(**Table 3**)

Table 3. Comparison of PUCAI score between mesalazine and non-mesalazine

Variables	PUCAI score		p-value
	Pre- treatment	Post- treatment	
Mesalazine	35 (10-75)	0	**0.007***
Non- Mesalazine	38 (20-65)	26 (10-25)	0.213

Discussion

Ulcerative colitis (UC) is a disease with a less heterogeneous phenotype than Crohn's disease (CD) but it still poses many unique challenges. The incidence of pediatric-onset UC, which constitutes roughly 15% to 20% of all UC, ranges from 1 to 4/100,000/year in most North American and European regions. It is extensive in 60% to 80% of all cases and twice as often as in adults. Since disease extent has been consistently associated with disease severity, it is not surprising that children with UC more often require hospitalization for an acute severe exacerbation (25%–30% over 3–4 years) and more often to undergo colectomy for medically refractory disease (up to 30%–40% in a 10-year follow-up), although lower colectomy rates have also been reported.[7]

It is mandated that the rapidly emerging novel therapies for inflammatory bowel diseases (IBDs) be evaluated in the clinical trial setting. Robust outcome measures are of utmost importance in determining the outcome of these trials. No single clinical or biochemical parameter consistently reflects activity of intestinal inflammation and, thus, multi-attribute measures of disease activity have been developed. Although other Crohn's disease (CD) activity indices have been used, the Crohn's Disease Activity Index (CDAI) is generally accepted as the standard clinical outcome measure in adult CD trials. Meanwhile, The Pediatric Crohn's Disease Activity Index (PCDAI) has become the most accepted disease activity measurement in childhood CD. [7]

In 2007, a Pediatric Ulcerative Colitis Activity Index (the PUCAI) was developed and validated using prospectively enrolled cohorts of children with UC. The PUCAI score

which lacks of invasive parameters, is suitable for longitudinal use in clinical trials and for determining the timely introduction of second-line therapy in severe acute UC.

The feasibility of using PUCAI in an outpatient clinical practice setting is also excellent. Over 96% of visits contained all six required components to calculate a PUCAI. The test-retest reliability of the PUCAI was also quite good. This study extends the foundational work completed by Turner, et al by including large sample size and diversity of practice sites (approximately 2000 patients from 35 centers). The PUCAI differentiated very well among the four PGA-based disease severity categories, with a fairly distinct separation between disease categories. The PUCAI change scores also differentiated well among different categories (no change, small, moderate, large) of change in PGA. A small change in PUCAI (indicated with a 10-point change) gave a sensitivity and specificity of approximately 80%.[8]

5-ASA acts topically on the colonic mucosa but is rapidly absorbed if ingested. As such. this drug is usually bound to an inactive carrier in order to prevent early absorption and metabolism within the small bowel. The covalent bond will be cleaved by bacterial diazoreductases, releasing the active form into the colon. Sulfasalazine, olsalazine and balsalazide are known to utilize this mechanism to ensure a more precise drug delivery to the colon. Meanwhile, another formulation of ASA, a pH-sensitive acrylic coated 5-ASA, works by delaying the release of its active compound until luminal pH of 7 in the distal bowel. This allows a bolus of 5-ASA to be released in the terminal ileum and proximal colon. Asacol and salofalk are known to employ this method. Latest formulations, such as Apriso and Lialda, utilize both a pH-sensitive acrylic layer to delay 5-ASA release and a coating of lipophilic and hydrophilic excipients to extend release throughout the colon.[9,10]

Four small pediatric clinical trials and a few retrospective studies confirmed that 5-ASA is effective for inducing remission in mild to moderate UC in children, achieving endoscopic remission in 27% after 12 weeks. There are no pediatric trials evaluating combined oral and rectal 5-ASAs, nor the effectiveness of 5-ASA in maintaining remission. The Cochrane meta-analysis showed a trend that suggest better benefit of the newer 5-ASA preparations (in terms of both efficacy and minimizing adverse effects) over sulfasalazine for inducing remission, but sulfasalazine was superior for maintaining remission. In contrast, the recent meta-analysis showed no difference in both inducing and maintaining remission. One pediatric double-blinded randomized clinical trial (RCT) showed that olsalazine 30 mg/ kg/ day induced a clinical response in 39% versus 79% with sulfasalazine 60 mg/ kg/ day after 3 months in 56 children with mild to moderate UC. Results from another pediatric trial suggested equivalent efficacy of mesalazine and sulfasalazine in maintaining remission in either UC or Crohn's colitis. A dedicated meta-analysis comparing the efficacy of sulfasalazine

versus newer 5-ASA included 20 RCTs and showed no major differences of efficacy and adverse events.[9]

In this study, it was shown that mesalazine therapy could significantly reduce PUCAI scores in children with ulcerative colitis. Several studies have shown that administering mesalazine to mild to moderate pediatric UC has low effectiveness. But the intention-to-treat 35% remission rate at week 6 is consistent with published data from other studies. Clinical remission in adults has been reported in only 28–46% of active patients. Comparisons between adult and pediatric results, however, are not straightforward. A PUCAI-defined remission is more difficult to achieve as compared with a Mayo-defined remission, used in the aforementioned adult trials. A Mayo-defined remission may still allow some blood in the stool. Pediatric data to benchmark our results are scarce. A small trial with only 15 patients in the 5-ASA arm had a similar PUCAI-defined remission rate of 35% at 8 weeks. Another pediatric trial found a PUCAI-defined remission rate of 40% in the standard-dose and 48% in the high-dose mesalazine groups, slightly higher than in our study.[6] However, that trial included a higher proportion of children with mild disease [25% of children in our trial versus ~50% in the aforementioned study]. A North American pediatric registry found that only 31% of children with UC treated with 5-ASA at disease onset were in steroid-free remission and had no treatment escalation at 1 year.[10]

According to the ESPGHAN-ECCO [European Society for Paediatric Gastroenterology Hepatology and Nutrition and European Crohn's and Colitis Organization] guidelines, 5-ASA is the first-line treatment in mild-moderate pediatric UC. However, pediatric gastroenterologists should be aware of the fact that patients may need to change to second-line treatment especially in children with PUCAI score of > 45 on day 3. Some studies show that mesalazine therapy takes 2–3 weeks for adequate response, as such, a lack of response by 3 weeks should trigger a change in treatment. This is consistent with our study which showed that the average treatment for ulcerative colitis was more than 3 weeks.[10]

Conclusion

Ulcerative colitis (UC) is a chronic relapsing inflammatory condition. UC is often treated with mesalazine as the first-line treatment. The use of the PUCAI score is an appropriate tool to determine the progression of this disease. Based on the data obtained, the administration of mesalazine therapy in children with ulcerative colitis can improve PUCAI scores compared to children who do not receive mesalazine therapy.

Conflict of Interest

None declared.

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