The role of mesalazine co-treatment in the prevention of recurrence in subjects with subclinical inflammatory bowel disease and perianal fistula who are scheduled for surgical intervention

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The role of mesalazine co-treatment in the prevention of recurrence in subjects with subclinical inflammatory bowel disease and perianal fistula who are scheduled for surgical intervention

AIM: *To investigate the impact of mesalazine co-treatment in addition to the surgical intervention on recurrence rate in subjects with subclinical inflammatory bowel disease (SIBD) who present with perianal fistula (PAF).*
MATERIALS AND METHODS: *All consecutive patients who had undergone surgery for PAF in our institutes were included in this retrospective analysis. Ileal tissue samples were obtained during colonoscopy for pathological evaluation. Patients with active chronic ileitis, structural distortion, erosion, ulceration, cryptitis, crypt abscess, fibrosis, and Paneth cell hyperplasia were defined as SIBD. Patients were divided into two groups according to the presence or absence of SIBD on pathological evaluation of ileal tissue samples (Group 1: SIBD +; Group 2: SIBD -). Rectal 5-aminosalicylic acid (mesalazine) of 2 gr once daily was administered to half of the subjects in each group for 8 weeks. The difference in 6 months recurrence rates of subjects receiving or not receiving mesalazine was the primary outcome measure.*
RESULTS: *The overall recurrence rate of subjects not receiving mesalazine was significantly higher than that of the subjects receiving mesalazine (9.7% vs. 4.4%, p = 0.020). Recurrence rate of the subjects with SIBD who received mesalazine co-treatment was significantly lower than those without mesalazine (1.6% vs. 12.6%, p=0.002). However, recurrence rate of the subjects without SIBD who received and not received mesalazine co-treatment was similar (6.8% vs. 7.8%, p=0.764).*
CONCLUSION: *Mesalazine co-treatment in addition to the surgical intervention was associated with lower 6 months recurrence rate compared to surgical intervention alone in patients with SIBD and PAF.*

KEY WORDS: Inflammatory bowel disease, Mesalazine, Perianal fistula

Introduction

Perianal fistulas (PAF) originating from anus and perianal soft tissue are of major concern due to the related morbidity caused by incontinence and consequently poor quality of life as a result of either the disease itself or the surgical interventions [1]. Persistent infection or ulceration of a mucosal defect which further penetrates through the wall of the anal canal and maintains by the mechanical forces resulting from fecal stream is the oldest concerning the pathogenesis of the fistula formation [2]. Other proposed mechanisms include infection in the anal glands which constitute an origin for the fistula formation and epithelial-to mesenchymal transition on a cellular level [3]. Increased transforming growth factor-b, interleukin-13 and increased matrix remodeling enzyme concentration support the idea that EMT plays a role in the development of perianal fistulas in patients with Crohn's disease.

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Although Crohn's disease is one of the most common causes of PAF formation, diverticulitis, sexually transmitted infections, rectal trauma, tuberculosis, anorectal cancer and HIV may be associated with the development of PAFs. On the other hand subclinical Crohn's disease and Crohn's disease-like ileitis may also be associated with PAF formation [4].

Mesalazine, which also refers to 5-aminosalicylic acid (5-ASA), is utilized in treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease [5]. Although the exact mechanism of action for mesalamine is not clear, anti-inflammatory properties of this agent is believed to reduce symptoms and recurrence in patients with inflammatory bowel disease. However, data concerning the role of mesalazine in the treatment of ileitis associated with subclinical inflammatory bowel disease (SIBD) is lacking.

The aim of this study was to investigate the impact of mesalazine co-treatment in addition to the surgical intervention on recurrence rate in subjects with SIBD who present with PAF.

Materials and Methods

All consecutive patients with who underwent diode laser thermocoagulation for perianal fistula in our institutes between February 2008 and May 2017 were included in this retrospective analysis. Patients with known inflammatory bowel diseases were excluded. All subjects underwent pelvic and MRI and colonoscopy. Ileal tissue samples were obtained during colonoscopy for pathological evaluation. Patients with active chronic ileitis, structural distortion, erosion, ulceration, cryptitis, crypt abscess, and fibrosis and Paneth cell hyperplasia were defined as SIBD.

Diode laser thermocoagulation was performed under spinal anestehesia for treatment of perianal fistula. All patients underwent mechanical bowel preparation with Fleet oral soda and Fleet enema and received 1 g cefuroxime and 500 mg metronidazole intravenously prior to surgery. Two more doses of intravenous 500 mg metronidazole was administered within the first 24 hours of the postoperative period. A FiLaCTM diode laser (Biolitec AG, Germany) was used in this study. Closure of the fistula tract by coagulation was achieved by slowly withdrawing the laser probe through the fistula tract at a rate of about 3 seconds per cm until the laser probe coagulates and closes the external opening of the fistula.

Patients were divided into two groups according to the presence or absence of subclinical inflammatory disease (SID) on pathological evaluation of ileal tissue samples (Group 1: SIBD +; Group 2: SIBD -). Rectal 5-aminosalicylic acid (mesalazine) of 2 gr once daily was administered to half of the subjects in each group for 8 weeks. The difference in 6 months recurrence rates of subjects receiving or not receiving mesalazine was the primary outcome measure of this study.

Table I - *Comparison of the two groups with respect to the mesalazine co-treatment.*

Variables		With Mesalazine treatment (n=250)	Without Mesalazine treatment (n=298)	P value
Age (years)		37.6 (9.4)	37.99 (10.3)	0.671
Sex	Male	194 (77.6%)	228 (76.5%)	0.872
	Female	56 (22.4%)	70 (23.5%)	
Microscopic signs	Yes	119 (47.6%)	119 (39.9%)	0.115
	No	134 (52.4%)	176 (60.1%)	
Recurrence	Yes	11 (4.4%)	29 (9.7%)	0.020
	No	239 (95.6%)	269 (90.3%)	

Table II - *Comparison of the recurrence rates with respect to the presence of subclinical inflammatory bowel disease and mesalazine co-treatment.*

	SIBD + and Mesalazine +n=119	SIBD + and Mesalazine -n=119	P value
Recurrence rate	2 (1.6%)	15 (12.6%)	0.002
	SIBD - and Mesalazine +n=131	SIBD - and Mesalazine -n=179	P value
Recurrence rate	9 (6.8%)	14 (7.8%)	0.764

Table III - *Predictors of recurrence after surgery for perianal fistula in patients with subclinical inflammatory bowel disease.*

Variable	Regression coefficient (B)	SE	OR	P value
Age	-0.004	0.16	0.996	0.796
Mesalazine therapy (Yes)	-1.527	0.399	0.217	<0.001
Microscopic signs (Yes)	-0.249	0.322	0.779	0.439

Statistical Analysis

Data normality was tested by Shapiro Wilk test. Continuous variables were summarized as mean (SD) while categorical variables were summarized as frequencies (percentages %). For comparison between the two groups in terms of categorical variables, chi-square test was used. Groups were compared using the student-t-test for continuous variables. Binary logistic regression analysis was conducted to test the predictors of recurrence. All analyses were done using the SPSS version 25 for windows.

Results

A total of 548 subjects were analyzed (mean age 37.8 ± 9.9 years, 77.6 % male). Pathological evaluation of the ileal biopsy samples revealed that 238 (43.4%) subjects had SIBD, while the rest 310 (56.6%) normal ileal biopsy. Recurrence at 6 moths was observed in 40 (7.2 %) subjects. 250 subjects (45.6 %) with and without SIBD received mesalazine treatment.

Recurrence rates of subjects with respect to the presence or absence of mesalazine treatment are presented in Table I. The overall recurrence rate of subjects not receiving mesalazine was significantly higher than that of the subjects receiving mesalazine (9.7% vs. 4.4%, p = 0.020). Recurrence rate of the subjects with SIBD who received mesalazine co-treatment was significantly lower than those without mesalazine (1.6% vs. 12.6%, p=0.002). However, recurrence rate of the subjects without SIBD who received and not received mesalazine co-treatment was similar (6.8% vs. 7.8%, p=0.764) (Table II). Logistic regression analysis revealed that mesalazine therapy was a significant predictor of recurrence. Patients who received mesalazine therapy had less risk of recurrence (OR=0.217) compared to those who did not receive mesalazine therapy (P<0.001) (Table III).

Discussion

The present study aimed to investigate whether mesalazine co-treatment in addition to the surgical interment provides favorable results concerning the recurrence rate compared to surgical intervention alone. Our findings show that mesalazine co-treatment in addition to the surgical intervention is associated with lower 6 months recurrence rate compared to surgical intervention alone. While the 6 months recurrence was significantly lower among subjects with SIBD who received mesalazine co-treatment compared to those without mesalazine co-treatment, 6 months recurrence rate among those without SIBD on ileal biopsies was similar either they have received or not received mesalazine co-treament in addition to the surgical intervention. When the whole study population was taken into consideration mesalazine co-treatment was associated with lower risk of recurrence at 6 months.

Perianal fistula is an abnormal communication between the anorectal tract and the perineal skin. PAFs are common during the course of Crohn's disease and results in significant morbidity, including scarring and fecal incontinence. However, a number of conditions including, diverticulitis, infections, trauma, tuberculosis, anorectal cancer and HIV may also be involved in the etiology of the PAFs [6]. Treatment of PAF includes combined aggressive medical therapy consisting of antibiotics, immunomodulators, and anti-tumor necrosis factor antibody and surgical interventions [7-11]. Despite strict preoperative preparing and proper surgical and medical management, patients with PAFs have a recurrence rate ranging between 7% and 50% [12]. Location and course of the PAF, failure to recognize the internal opening and overall structure of the fistula tract, inappropriate surgical technique, lack of experience, and failure to get rid of the entire tract along with its ramifications are all associated with increased recurrence rates in patient with PAF [13].

Several agents used in combination with surgical interventions have demonstrated promising efficacy in the prevention of recurrences and management of fistulising inflammatory bowel disease. Present and colleagues have shown in 94 adult patients with Crohn's disease who had draining abdominal or perianal fistulas that infliximab, a tumor necrosis factor alfa antibody, facilitates the closeure of PAFs compared to placebo [14]. Other reports including patients with ulcerative colitis supported the efficacy of infliximab in the treatment of fistulas in patients with inflammatory bowel diseases [15].

Mesalazine is a 5-ASA compound used in induction and maintenance therapy of ulcerative colitis. Following the interaction with the damaged endothelium, 5-ASA is converted to acetyl-5-ASA, then absorbed and excreted into the urine or stool. The mechanism of action mesalazine includes inhibition of IL-1, IL-2, rumor necrosis factor alfa production, and T-cell proliferation, altering cell adhesion expression pattern, inhibiting antibody production and mast cell release, and interfering with macrophage and neutrophil chemotaxis [16].

Mesalazine also induces lymphocyte apoptosis and regulates NF-κB [17,18]. Substantial amount of data have shown that mesalazine can be useful in induction and maintenance therapy of patients with inflammatory bowel diseases [19-21]. However, data concerning the role of mesalazine on the recurrence rates following surgical intervention for PAF in patients with SIBD is lacking. Our study, for the first time shows that mesalazine co-treatment in addition to the surgical intervention may reduce the risk of recurrence at 6 months in patient with SIBD and PAF. Although the exact mechanism how mesalazine reduce recurrence in patients with SIBD and PAF is unclear, considering the positive effects of

mesalazine in induction and maintenance therapy of patients with inflammatory bowel diseases, we speculate that mesalazine reduces inflammation in perianal region through its antinflammatory properties. Nevertheless, further randomized, prospective studies are required to clearly address the role of mesalazine in the management of PAFs in patients with SIBD.

Conclusion

In conclusion, mesalazine co-treatment in addition to the surgical intervention is associated with lower 6 months recurrence rate compared to surgical intervention alone in patients with SIBD and PAF.

Riassunto

Scopo di questo studio retrospettivo è stato quello di indagare l'impatto del co-trattamento con mesalazina oltre all'intervento chirurgico sul tasso di recidiva in soggetti con malattia infiammatoria intestinale subclinica (SIBD) che presentano fistola perianale (PAF).
Sono stati inclusi in questa analisi retrospettiva tutti i pazienti consecutivi che avevano subito un intervento chirurgico per PAF nel nostro istituto. Campioni di tessuto ileale sono stati ottenuti durante la colonscopia per la valutazione patologica. I pazienti con ileite cronica attiva, distorsione strutturale, erosione, ulcerazione, criptite, ascesso della cripta, fibrosi e iperplasia delle cellule di Paneth sono stati definiti come SIBD. I pazienti sono stati divisi in due gruppi in base alla presenza o assenza di SIBD sulla valutazione patologica di campioni di tessuto ileale (Gruppo 1: SIBD +; Gruppo 2: SIBD -). A metà dei soggetti di ciascun gruppo è stato somministrato per via rettale 2 g di Acido 5-aminosalicilico (mesalazina) una volta al giorno per 8 settimane. La differenza nei tassi di recidiva a 6 mesi dei soggetti che ricevevano o non ricevevano mesalazina ha rappresentato la misura primaria dell'esito.
Risultati: il tasso di recidiva complessivo dei soggetti che non ricevevano mesalazina è risultato significativamente più alto di quello dei soggetti che ricevevano mesalazina (9,7% contro 4,4%, p = 0,020). Il tasso di recidiva dei soggetti con SIBD che hanno ricevuto il co-trattamento con mesalazina è stato significativamente inferiore rispetto a quelli senza mesalazina (1,6% vs. 12,6%, p = 0,002). Tuttavia, il tasso di recidiva dei soggetti senza SIBD che hanno ricevuto e non hanno ricevuto il co-trattamento con mesalazina è stato simile (6,8% vs 7,8%, p = 0,764).
Conclusione: il co-trattamento con mesalazina in aggiunta all'intervento chirurgico è stato associato a un tasso di recidiva inferiore a 6 mesi rispetto al solo intervento chirurgico nei pazienti con SIBD e PAF.

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