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To compare non-invasive markers like fecal calprotectin, c-reactive protein, crohn's disease activity index (CDAI), total leukocyte count with the simple endoscopic score in crohn's disease in assessing activity of crohn's disease

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Abstract
Introduction: The diagnosis of CD is established with clinical, endoscopic, histological and imaging studies of the bowel. Various markers have been proposed to objectively evaluate disease activity, but sensitivity and specificity have been a concern for each. A combination of biomarkers may be the most useful for prediction or confirmation of clinical disease activity and endoscopically visible inflammation.
Aims & Objective: The aim of study was to compare non-invasive markers like fecal calprotectin, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Crohn's disease activity index (CDAI), blood leukocytes count with the simple endoscopic score in assessing activity of Crohn's disease (CD).
Material & Methods: All Crohn's patients undergoing ileocolonoscopy were enrolled in our study. The sample size calculated for the present study was 45 patients. SES-CD score was calculated after ileocolonoscopy, Fecal calprotectin test, Blood sample for leukocyte count and CRP was done in all patients, CDAI is calculated. All laboratory parameters were correlated with SES-CD. The data was analysed by IBM SPSS Statistics 20 version.
Results: Out of 45 patients, 28 were male.. Mean age of patients were 35.08 years, and median duration of disease was 65.71 months. According to Montreal classification, the distribution was age at onset A1:A2:A3 0:30:15, location of disease L1:L2:L3 11:05:29, behaviour of disease B1:B2:B3 26:07:02. According to SES-CD score patients was divided into four groups. Inactive subgroup (SES-CD score <3) were 6, mild activity (SES-CD score 4-10) was observed in 10 patients. Moderate activity (SES-CD score 11-19) was seen in 20 patients. 9 patients had severe activity (SES-CD score >20). Fecal calprotectin was positive in 3/6 patients in inactive subgroup, 10/10 in mild subgroup,20/20 in moderate subgroup,9/9 in severe subgroup. C-reactive protein was positive in 3 cases of mild subgroup of SES-CD, 18 cases of moderate subgroup and 9 cases of severe subgroup of SES-CD. CRP was negative in inactive subgroup. Scatter plot demonstrates the positive correlation with SES-CD score.Mean CRP in inactive subgroup was 3.66±0.81, mild 5.7±2.86, moderate 75.1±32.41, severe 176.22±26.29 which is statistically significant (<0.001). CRP is helpful in differentiating mild activity from moderate activity, moderate activity from severe activity; however it is not helpful in discriminating inactive from mild disease activity.
ESR was positive in 6 patients of moderate subgroup and 8 of severe subgroup of patients which is statistically significant (<0.001), however it is negative in inactive and mild subgroup of patients. Total leucocyte count was positive in 4/20 in moderate subgroup, 8/9 in severe subgroup which is statistically significant (<0.001). Total leucocyte count was negative in inactive and mild subgroup of patients. TLC could neither discriminate inactive from mild nor mild from moderate endoscopic activity. CDAI was positive in 9/45 patients which is statistically significant (<0.001) in discriminating moderate from severe activity.
Conclusions: Fecal Calprotectin is superior to all non-invasive tests for identifying inactive disease activity. It has closest correlation to SES-CD. Fecal calprotectin was positive in 93.3% of patients which is highest for any non –invasive marker. CRP helps in differentiating mildly active from moderate and severely active disease. ESR helps in differentiating moderate active from severely active disease. CDAI is less effective in identifying the disease activity.

Keywords: crohns disease, fecal calprotectin, CRP, ESR, SES-CD, CDAI

Introduction

Crohn's disease (CD) is a relapsing systemic inflammatory disease; mainly affecting the gastrointestinal tract with extra intestinal manifestations [1]. Inflammatory bowel disease is traditionally thought to be uncommon in India; however recent scenario shows an increasing trend [2]. The assessment of Crohn's disease activity is based on a combination of symptoms, clinical findings, and endoscopy. Ileocolonoscopy is the gold standard for assessment of intestinal inflammation. It has a disadvantage of being invasive, expensive, time consuming, and sometimes uncomfortable for patients [3].

To overcome these limitations, several laboratory markers have been evaluated regarding their performance for monitoring CD activity. Acute-phase reaction and migration of leukocytes to the gut is seen during active inflammation in CD. Hence, various proteins can be measured in serum and feces of the patients. C-reactive protein (CRP), Fecal Lactoferrin and Fecal Calprotectin can be measured for assessment of disease activity [4].

Calprotectin is a heterodimer small calcium-binding protein and member of the S100 family of zinc-binding proteins. Fecal calprotectin represents 60 % of cytosolic proteins in granulocytes. The amount of calprotectin in feces is

therefore proportional to the neutrophil migration to the gastrointestinal mucosa, hence it can be used for monitoring disease activity [5]. It accurately distinguishes IBD from non-IBDs such as irritable bowel syndrome. A good correlation between fecal calprotectin and the Crohn's Disease Endoscopic Index of Severity has already been demonstrated [6]. Crohn's Disease Endoscopic Index of Severity is cumbersome to complete and time-consuming in clinical practice; therefore, the Simple Endoscopic Score for Crohn's disease (SES-CD) was developed and validated.

SES-CD is much easier to perform Compared with the Crohn's Disease Endoscopic Index of Severity, therefore frequently used in clinical practice. Data regarding the correlation of fecal calprotectin with SES-CD are scarce, and there is especially a paucity of studies evaluating the endoscopic disease activity with calprotectin in relation to other biomarkers [7, 8]. There is paucity of studies from India comparing non- invasive biomarkers with SES-CD in Crohn's disease; hence this study is intended to compare the non-invasive markers like fecal calprotectin, CRP,ESR, CDAI, Blood leukocyte count with SES –CD in assessing activity of Crohn's disease.

Aims and Objectives

The aim of study is to compare non-invasive markers like fecal calprotectin, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Crohn's disease activity index (CDAI), blood leukocytes count with the simple endoscopic score in assessing activity of Crohn's disease (CD).

Materials and Methods

This Single centre Prospective, descriptive study was conducted in the Department of Gastroenterology Medical Trust hospital, Kochi – Kerala, India. which is a tertiary care referral centre over a period of two year from May 2015 – April 2017 following its approval by the Institutional ethical committee. All diagnosed cases of Crohns disease patients undergoing Colonoscopy were enrolled, based on standard clinical, endoscopic, and histological criteria. Written informed consent was obtained from patients or their legal surrogates before enrollment. The sample size calculated for the present study was 45 patients.

Inclusion Criteria

All Diagnosed cases of Crohn's disease were enrolled.

1. Complete ileocolonoscopy including biopsies (at least two biopsies from terminal ileum and four colonic biopsies from affected regions)
2. Fecal samples delivered before ileocolonoscopy (bowel preparation was not started until the fecal specimen was delivered).
3. Blood samples collected before ileocolonoscopy.

Exclusion Criteria

1. Incomplete ileocolonoscopy (ileum not intubated).
2. Infectious enterocolitis (positive stool culture for Salmonella, Shigella, Campylobacter)
3. Colorectal cancer
4. Ulcerative colitis
5. Inability to collect fecal samples.
6. History of extensive bowel resection (ileosigmoidostomy and ileorectostomy)
7. Regular intake of aspirin and / or non-steroidal anti-inflammatory drugs (NSAID) (more than two tablets per week)

Data Collection

All Crohn's patients undergoing ileocolonoscopy were enrolled in our study. SES-CD score was calculated after ileocolonoscopy, Fecal calprotectin test, Blood sample for leukocyte count and CRP was done in all patients, CDAI is calculated. All laboratory parameters were correlated with SES-CD. The data was analysis was by IBM SPSS Statistics 20 version.

For calculating the SES-CD, the intestine was divided into five segments: the ileum, the right colon, the transverse colon, the left colon, and the rectum. The degree of disease involvement in each of the five segments was determined by the assessment of four parameters:

Presence and size of ulcers (score 0 – 3),
Extent of ulcerated surface (score 0 – 3),
Extent of affected surface (score 0 – 3),
Presence and type of narrowing (score 0 – 3).

The clinical disease activity was assessed by the measurement of the CDAI.

Fecal calprotectin was measured by fecal calprotectin antigen strip test. The test result must be read within 10 min. Blood leukocyte count, ESR and CRP were measured. Total Leukocyte count was said to be positive >11, 000/dl. ESR is taken as positive if >20 mm of Hg/hr. CRP is said to be positive if >3mg/dl

Table 1: Simple Endoscopic Score –Crohn's Disease

Simple endoscopic score (SES-CD)				
		SES Score		
Variable	**0**	**1**	**2**	**3**
Size of ulcers (cm)	**None**	**Aphthous ulcers (diameter 0.1-0.5)**	**Large ulcers (diameter 0.5-2)**	**Very large ulcers (diameter > 2)**
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	<50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD = sum of all variables for the 5 bowel segments.
Values are given to each variable for every examined bowel segment
Source: Daperno, M. *et al*. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest. Endosc. 60, 505-512 (2004).

The sum of the score for each endoscopic variable ranges from 0 to 15, except for stenosis, where it varies between 0 and 11, because 3 represents a stenosis through which a colonoscope cannot be passed, and therefore can be observed only once. The lowest possible SES-CD was 0, representing an intestine without any lesions, the highest possible score was 56 points.

In the majority of studies on SES-CD, CD severity was

defined as inactive when SES-CD was 0–2; mild when 3–6; moderate 7–15; and severe >16.

Table 2: Crohn's Disease Activity Index (CDAI)

Crohn's Disease Activity Index	
Number of liquid stools (daily for 7 days)	x 2
Abdominal pain (none = 0, mild = 1, moderate = 2, severe = 3)	x 5
Sense of well-being (well = 0, slightly below par = 1, poor = 2, very poor = 4, terrible = 4)	x 7
Number of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula or abscess, fever > 37.8° C)	x 20
Taking diphenoxylate or loperamide (no = 0, yes = 1)	x 30
Abdominal mass (no = 0, questionable = 1, present = 5)	x 10
Hematocrit (males: 47 – HT%, females: 42 – Ht%	x 6
Weight (1 – weight / standard weight x 100). Add or subtract according to the sign	x 1
Total	

Results and Observations

Table 3: Gender wise distribution of patients

Sex	No of Patients
Male	28
Female	17

Male to Female ratio in our study on CD patients is 1.6:1

Table 4: Demographic characteristics of CD patients

Demographic characteristics	Total (45)
Mean Age (Years)	35.08
Mean BMI (Kg/m^2)	20.43
Median Duration of Disease (Months)	65.71

Mean age of patients were 35.08 years, Mean BMI of patients was 20.43 Median duration of disease is 65.71 months.

Table 5: Distribution of disease extent as per age.

CD	Age Group (yrs)			Total
	≤ 16	17- 40	> 40	N
Ileum	0	9	2	11
Colon	0	2	3	5
Ileum +Colon	0	19	10	29
Total-N (%)	0	30	15	45

Majority of patients 31 (68.8%) belong to age group 17-40 years. Isolated SI disease is more common 9/11 (67%) in age group 17-40 years. Isolated colon involvement seen in 5 patients. Ileum +Colon involvement is most commonly involved area in Ileocolonoscopy

Table 6: Behaviour/ Course of CD

Disease Behavior	No of Patients
B1-Non Stricturing/Non Penetrating	36
B2-Stricturing disease	**7**
B3-Penetrating disease	2
Total	45

Most CD patients 36 have B1: Non-stricturing, non-penetrating disease.
Stricturing disease (B2) is seen in 7 patients. 2 patients had penetrating disease.

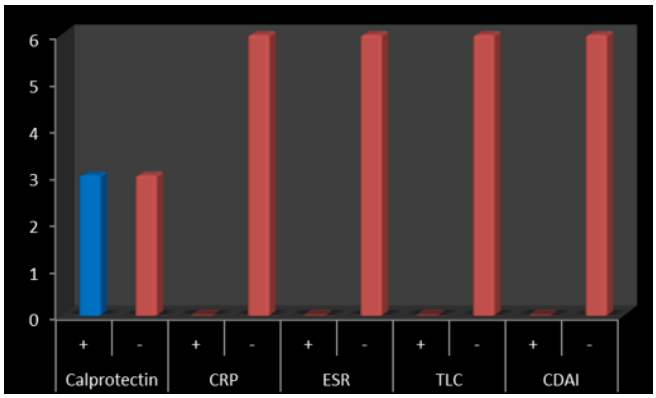

Fig 1: Correlation of Inactive SES-CD subgroup with Fecal Calprotectin, CRP, ESR, Total Leukocyte Count and CDAI

Above Fig shows Fecal calprotectin is only parameter which is positive in 3 patients with Inactive Disease activity on Endoscopic Evaluation (SES-CD score 0-3). CRP, ESR, TLC, CDAI were negative in Inactive Disease activity.

Table 7: Simple Endoscopic Score V/s Fecal Calprotectin

		SES-CD			
		Inactive	Mild	Moderate	Severe
Calprotectin	+ ve	3	10	20	9
	- ve	3	0	0	0

Fecal calprotectin (qualitative) is positive in 42/45 patients. It is 100% positive in mild, moderate and severe active subgroups of simple endoscopic score. In inactive subgroup it has 50% negativity for diagnosis Crohn's disease.

Table 8: Simple Endoscopic Score-CD V/s C - reactive protein (CRP)

		SES-CD			
		Inactive	Mild	Moderate	Severe
CRP	- ve	6	7	2	0
	+ ve	0	3	18	9

C- Reactive protein was positive in 3 cases of mild subgroup of SES-CD, 18 cases of moderate subgroup and 9 cases of severe subgroup of SES-CD.CRP was negative in inactive subgroup.

Table 9: Simple Endoscopic Score-CD V/s Erythrocyte Sedimentaion Rate.

		SES-CD			
		Inactive	**Mild**	**Moderate**	**Severe**
ESR	- ve	6	10	14	1
	+ ve	0	0	6	8

ESR is positive in total of 14 patients out of 45 cases. ESR is negative in inactive and mild disease activity. ESR helps do differentiate moderate from severe disease, which is statistically significant.

Table 10: Simple Endoscopic Score V/s Total Leukocyte Count

		SES_CD			
		Inactive	**Mild**	**Moderate**	**Severe**
Leukocyte	-ve	6	10	16	1
	+ve	0	0	4	8

Total Leukocyte count was positive in 12/45 cases. It has no predictive value in identifying inactive and mild disease activity.

Table 11: Simple endoscopic score V/s Crohn's Disease Activity Index

		SES_CD			
		Inactive	**Mild**	**Moderate**	**Severe**
CDAI	-ve	6	10	18	2
	+ve	0	0	2	7

CDAI was positive in 9/45 patients

Table 12: Clinical and laboratory characteristics at baseline of CD patients

	No	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**	**Chi Square Test**	**P Value**
SES-CD	45	3.00	25.00	12.2889	7.04409		
CDAI	45	46.00	330.00	133.0000	66.43965	24.02	<**0.001**
CRP	45	3.00	220.00	70.3778	66.63683	27.45	<**0.001**
TLC	45	4500.00	20000.00	9281.3333	4166.99783	24.091	<**0.001**

In the present study the minimum value of SES-CD was 3 and maximum value was 25. Mean CDAI was 133, minimum value was 46 and maximum was 330, which was statistically significant. Mean CRP was 70.37, minimum value was 3mg/dl and maximum value was 220mg/dl, which was statistically significant. TLC was statistically significant in present study, the minimum value was 4500 and the maximum value was 20,000.

Table 13: Correlation of the Simple endoscopic score for Crohn's disease (SES-CD) subgroups with the CDAI, CRP, Total Leukocytes Count

Endoscopic activity	**Inactive (0-3)**	**Mild (4-10)**	**Moderate (11-19)**	**High (≥20)**
No of patients	6	10	20	9
CDAI	71.33±71.38	94.4±69	125±66.43	234.55±71.79
P- value	0.5328 0.2501 <0.001			
CRP	3.66±0.81	5.7±2.86	75.1±32.41	176..22±26.29
P-value	0.1140 <0.001<0.001			
TLC	6148.33±719.17	6946±1637	8435±2770	1584±3169
P-value	0.2820 0.1298 < 0.001			
ESR	12.16±3.125	13.4±2.16	17.25±7.96	34.77±11.08
P-value	0.3628 0.1474 <0.001			

In the present study CDAI helps in differentiating moderate from severe disease activity and is statistically significant. CRP is also statistically significant in differentiating mild from moderate, moderate from severe disease activity. TLC can differentiate moderate from severe disease activity. ESR also statistically significant in differentiating moderate from severe disease activity.

Discussion

Male to Female ratio was 1.6. Male to female ratio in the national survey was 1.3 in CD[2]. In the present study, a slight male preponderance was noted.

Abdomen pain (87%) and diarrhea (78%) were common which is comparable with study done by Das *et al*. [9] Results from the Montreal classification were as follows, age at onset: A1(<16):A2(17-40):A3(>40) 0:30:15,location of disease L1(Ileum):L2(Colon):L3(Ileum+Colon) 11:05:29 which is similar to the study of Das *et al*. [9] The phenotype of Crohn's disease in India appears to be similar to that described in other regions of Asia and the West.

Mean BMI of CD patients were 20.43 kg/m^2. Mean age of CD patients 35.08 years, this result is similar to the results of the national survey.[2] In national survey, median duration of illness in patients with CD was 48 months.[2] In present study, median duration is 65.71 months.

The most common pattern of disease extent was involvement of both small and large intestine which was seen in 64.4% followed by isolated ileum involvement in 24.44% and isolated colon involvement was seen in 11%. This is with proportionate with the National study [4]. Perianal disease (perianal fistula and/or abscess) was noted in 10/45 (22%) patients.

All patients underwent ileocolonoscopy. SES-CD score was calculated in all of these individuals. Inactive disease activity (SES-CD score 0-3) was noticed in 6 patients. Mild activity (SES-CD score 4-10) was observed in 10 patients. Moderate activity (SES-CD score 11-19) was seen in 20 patients. 9 patients had severe activity (SES-CD score >20). Schoepfer [10]. *et al*. in his study had predominantly inactive and severely active patients (80%) compared to moderate. We had predominantly moderately active patients (44%).

Various studies have already shown that fecal calprotectin correlates to the endoscopic disease activity in CD patients. However, studies assessing the correlation between a grouped endoscopic disease activity according the SES-CD and fecal calprotectin are scarce from India. A study done from India by Samant H *et al*. [11] on 31 CD patients, median level of fecal calprotectin was 619 μg/g. 86.9% patients had

fecal calprotectin value >200 µg/g. A cut off of 30 µg/g had 100% sensitivity in discriminating active CD from IBS in the study of Tibble [12] and colleagues. The pooled sensitivity and specificity of FC was found to be as high as 93% and 96%, respectively [11]. In the present study we used a monoclonal antibody based immunoassay test for the detection of fecal calprotectin, which was positive in 42/45 patients. Compared to most of the study our study had a limitation of not being quantitative for estimation of fecal calprotectin.

Fecal calprotectin was positive in 3/6 patients in inactive subgroup,10/10 in mild subgroup,20/20 in moderate subgroup,9/9 in severe subgroup. Fecal calprotectin has closer association than the CRP, ESR, TLC, CDAI which is comparable to study conducted by Schoepfer and Sipponen.

C-reactive protein was positive in 3 cases of mild subgroup of SES-CD, 18 cases of moderate subgroup and 9 cases of severe subgroup of SES-CD. CRP was negative in inactive subgroup. Scatter plot demonstrates the positive correlation with SES-CD score. Mean CRP in inactive subgroup was 3.66±0.81, mild 5.7±2.86, moderate 75.1±32.41, severe 176.22±26.29 which is statistically significant (<0.001) and is comparable to Fagan *et al*. study [13]. CRP is helpful in differentiating mild activity from moderate activity, moderate activity from severe activity; however it is not helpful in discriminating inactive from mild disease activity.

ESR was positive in 6 of moderate subgroup and 8 of severe subgroup of patients which is statistically significant (<0.001), however it is negative in inactive and mild subgroup of patients. Scatter plot demonstrates the positive correlation with SES-CD score. Tibble [14] in his study on 22 patients with CD patients found ESR was statistically significant elevated compared to controls. ESR is could neither discriminate inactive from mild nor mild from moderate endoscopic activity.

Total leukocyte count was positive in 4/20 in moderate subgroup, 8/9 in severe subgroup which is statistically significant (<0.001). Total leukocyte count was negative in inactive and mild subgroup of patients. Scatter plot demonstrates the positive correlation with SES-CD score. TLC could neither discriminate inactive from mild nor mild from moderate endoscopic activity which is comparable to Schoepfer *et al* study [10].

CDAI was positive in 9/45 patients which is statistically significant (<0.001) in discriminating moderate from severe activity. The CDAI could neither discriminate inactive from mild nor mild from moderate endoscopic activity which has similar result done by Schoepfer study [10].

Conclusion

Fecal Calprotectin is superior to all non-invasive tests for identifying inactive disease activity. It has closest correlation to SES-CD. Fecal calprotectin was positive in 93.3% of patients which is highest for any non –invasive marker. CRP helps in differentiating mildly active from moderate and severely active disease. ESR helps in differentiating moderate active from severely active disease. CDAI is less effective in identifying the disease activity.

Limitation of study

The sample size in our study was relatively small and this might not be representative of population. A larger cohort is required for complete analysis on clinical, endoscopic and laboratory parameters in Crohn's disease. As our study does not involve control group, we could not calculate the sensitivity and specificity of non-invasive markers to that of SES-CD. In this study fecal calprotectin was a qualitative test hence we could not get the range of values in each sub group of SES-CD.

Recommendations

1. Fecal Calprotectin is superior to all non-invasive tests for identifying inactive disease activity. It has closest correlation to SES-CD; hence it can be used in follow up of patients in Outpatient department.
2. Fecal Calprotectin helps in diagnosing relapse of CD.
3. CRP is also a better test in distinguishing mild from moderate disease activity.
4. Fecal Calprotectin helps in distinguishing IBD from IBS.

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