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Serum procalcitonin as a prognostic marker in acute severe ulcerative colitis: a prospective study

Shubhra **MISHRA**[1], Sant **RAM**[2], Kaushal K **PRASAD**[1], Arun K **SHARMA**[1], Usha **DUTTA**[1] and Vishal **SHARMA**[1]

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ABSTRACT – **Background** – Procalcitonin may be increased in active ulcerative colitis (UC). We investigated the role of procalcitonin in predicting response in acute severe UC (ASUC). **Methods –** Consecutive patients with ASUC diagnosed on basis of Truelove and Witts criteria were enrolled. Serum procalcitonin levels for consecutive patients were measured at admission and day 3. We assessed role of procalcitonin values at presentation and at day 3 in assessing response on day 3 (Oxford's criteria) and need for second line therapy (day 28). **Results –** Of fifty patients (23 males, mean age: 35.98±13.8 years), 16 did not respond (day 3). Ten (20%) patients required second-line therapy. Baseline procalcitonin was significantly associated with response on day 3 (*P*=0.016). There was no association between day 1 or day 3 procalcitonin and need for second-line rescue therapy. **Conclusion –** Serial procalcitonin is not an effective biomarker for predicting outcomes or need for second line therapy in ASUC.

Keywords – Inflammatory bowel disease; colectomy; surgery; outcomes; ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease which usually has a relapsing remitting course[1]. Acute severe ulcerative colitis (ASUC) is a severe presentation of the disease and requires aggressive medical therapy or colectomy[2]. Up to 25% of patients with UC experience at least one episode of ASC in their lifetime[3,4]. Mortality from ASUC has drastically decreased with the use of corticosteroids in such patients, however a third of all patients may not respond to medical therapy and need an urgent colectomy[5]. Oxford's criteria has been used extensively to predict the risk of colectomy, but its components are subjective (stool frequency) and correlate poorly with mucosal inflammation[6]. Many parameters and composite scores have been evaluated for accurate prediction of response to medical therapy[7,8]. As the armamentarium of drugs available for medical therapy expands, it is important to timely recognize patients who may not respond to intravenous corticosteroids and may benefit from early institution of second line medical rescue therapy.

Procalcitonin is a peptide molecule which is a precursor of the endocrine hormone calcitonin. Calcitonin is primarily synthesized in the C cells of the thyroid gland and plays a regulatory role in calcium homeostasis. In patients with acute inflammation, there is an increased concentration of procalcitonin in the circulation[9]. This is attributed to an increased synthesis of procalcitonin across many extra thyroid organs as well as decreased cleavage of procalcitonin to calcitonin molecule[10]. Initially used as a biomarker of gram-negative infections, application of procalcitonin has gradually expanded to prognostication of other inflammatory diseases as well[11-13]. It is a useful tool to differentiate infective gastroenteritis from a flare of UC[14]. Although level of procalcitonin in patients with UC does not increase to the same extent as in patients with infective colitis, it is an effective marker for differentiating a severe flare from mild and moderately active disease[15]. Procalcitonin has been evaluated as a predictor of outcomes in patients with ASUC previously. Baseline procalcitonin was 73% accurate in predicting intravenous corticosteroid failure when a cut off of 0.1 mcg/mL was taken[16]. It correlated positively with the baseline UCEIS score and could be incorporated effectively into a model to predict response to intravenous corticosteroids[16].

The purpose of this study was to evaluate the role of procalcitonin as a biomarker for the severity of disease in patients who presented with ASUC and to assess its accuracy in predicting the response to intravenous corticosteroids and need for second line therapy.

METHODS

We have previously reported a randomised controlled trial at our center to evaluate the added impact of intravenous antibiotics (ceftriaxone and metronidazole) as compared to standard of care in patients with acute severe ulcerative colitis. The present report includes the same subset for whom we report the association between serum procalcitonin at admission and at day 3 with outcomes in these patients[17]. The study included patients admitted with a diagnosis of acute severe ulcerative colitis at a tertiary center from 1st April 2019 to 4th March 2020. Written informed consent was taken from all patients prior to inclusion and the study was approved by the Institute Ethics Committee, the work vide letter no NK/3148/Res/32.

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[1] Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. [2] Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
Corresponding author: Vishal Sharma. E-mail: sharma.vishal@pgimer.edu.in

Patients

Patients with active colitis (presence of blood mixed stools) were screened and those with ASUC, as defined by the modified Truelove and Witt's criteria were evaluated further. Thus, our study included patients who presented six or more bloody stools per day with one or more of the following: pulse rate >90/min, temperature >37.8 C, hemoglobin <10.5 g/dL, erythrocyte sedimentation rate >30mm at 1 hour or C-reactive protein >30 mg/L. Patients with age <12 years, had suspicion or evidence of infection or sepsis, toxic megacolon, patients with chronic uncontrolled comorbidities, pregnant or lactating mothers were excluded.

All patients received the standard of treatment including intravenous methylprednisolone 60 mg once daily, anticoagulation prophylaxis, intravenous fluids and were allowed orally on a soft diet. Since the patients were enrolled from a RCT[17], antibiotic regime was decided by randomization. In addition to the standard of treatment mentioned above, half of the patients received intravenous ceftriaxone 1 gm twice a day and metronidazole 500 mg thrice a day, while the other half received placebo infusions. Clinical features of all patients were noted, including the stool frequency, severity of bleeding, presence of toxic symptoms and baseline disease characteristics. Blood and stool investigations were done on admission, including inflammatory biomarkers: serum C-reactive protein, serum procalcitonin and fecal calprotectin. All patients underwent an unprepared sigmoidoscopy with rectal biopsy. Plain abdomen X-ray was done to rule out megacolon and perforation.

Response to treatment was assessed on day 3 as per the Oxford criteria[18]. Patients who had a partial or no response were managed according to the treating physician's discretion and the patient's choice. Second line rescue therapies which were offered included intravenous infliximab (5 mg/kg), intravenous cyclosporine (2 mg/kg/day) given once daily for five days or colectomy. Patients who responded to intravenous corticosteroids were discharged on oral prednisolone (40 mg/day) and azathioprine. Patients who were successfully treated with cyclosporine were subsequently prescribed oral cyclosporine (4 mg/kg) and azathioprine. Patients were followed up for 4 weeks after discharge from the hospital.

Measurement of serum procalcitonin

Procalcitonin was measured on admission which was taken as day 1, and at day 3 of therapy with intravenous corticosteroids. Non heparinized blood samples were drawn in pyrogen free polypropylene tubes. Samples were stored at room temperature and were processed within 6 hours of collection. In the event of delay in processing, samples were stored at -20°C. Samples containing precipitates were centrifuged before performing the assay. Serum procalcitonin levels were measured via electrochemiluminescence immunoassay (Elecsys BRAHMS PCT, Cobas E; Roche diagnostics, Switzerland) according to the manufacturer's instructions. Measurement range for the assay if from 0.02 ng/mL to 100 ng/mL.

Outcomes

Primary outcome was the response on day 3 as per the Oxford criteria. Secondary outcome was the need for second line rescue therapy.

Baseline procalcitonin levels were compared between those who had a complete response on day 3 and those who did not. Both day 1 and day 3 procalcitonin levels were compared between patients who eventually required second line therapy and those who responded. Day 1 and day 3 procalcitonin levels were also compared between patients who received antibiotic therapy and those recieving placebo infusions. Receiver operating characteristic (ROC) curve was plotted to analyse the accuracy of baseline procalcitonin for predicting non response and need for second line therapy.

Statistical analysis

Data entry and analysis was done using SPSS 20.0 software. Continuous variables were expressed using mean with standard deviation or median and IQR. Qualitative variables were expressed as proportions. Mann Whitney U test was used to compare quantitative data between two groups. *P* value <0.05 was considered statistically significant.

RESULTS

Fifty patients enrolled (23 males, mean age: 35.98±13.8 years). Mean disease duration was 41.1 (48.7) months. Baseline features of the cohort are described in TABLE 1.

TABLE 1. Baseline characteristics of the patients.

Parameter	Total (n=50)
Age (years)	35.98±13.8
Male	22 (44%)
Disease duration (months)	41.11 (48.17)
Extensive colitis (n, %)	22 (50%)
First presentation (n, %)	13 (26%)
Previous UC related hospitalization (n, %)	19 (38%)
Steroid used previously	23 (46%)
Azathioprine used	12 (24%)
Endoscopic Mayo score	2.68 (0.47)
Partial Mayo score	7.44 (0.97)
Complete Mayo score	10.1 (1.13)
Fulminant disease	23 (46%)
Severe Mayo	17 (34%)
Laboratory parameters	
Hemoglobin (gm/dL)	9.99±2.9
Total leucocyte count (cells/μL)	8586±3513
S.Creatinine (mg/dL)	0.68±0.189
S. albumin (mg/dL)	3.2±0.86
ESR (mm/h)	49.48±20.49
C reactive protein (mg/L)	51.8±112.6
Fecal calprotectin (μg/gm)	784.64±343.18

UC: ulcerative colitis; ESR: erythrocyte sedimentation rate.

Complete response at day 3 was observed in 13 (26%), partial response in 21 (42%) and no response in 16 (32%) patients. Twenty-seven of partial/non-responder patients responded to steroids with the median time to response being five[4-6] days. Ten patients required second line rescue therapy, of which seven were given intravenous cyclosporine while three patients underwent colectomy. None of the patients opted for infliximab, primarily due to financial constraints.

Role of procalcitonin in acute severe ulcerative colitis

Serum procalcitonin concentration in the serum was measured on day 1 and day 3 of intravenous corticosteroid therapy. Median procalcitonin level on admission of all patients was 0.049 [0.02–0.122] µg/L. The median procalcitonin on day 3 was 0.057 [0.021–0.114].

Prediction of response on day 3 as per Oxford day 1 procalcitonin was significantly higher in patients who showed no response on day 3. Median baseline procalcitonin level in non-responders was 0.098 [0.031–0.217] while it was 0.03 [0.02–0.095] µg/L in patients who had a partial or complete response (*P*=0.016). Four out of sixteen non-responders had procalcitonin >0.1 µg/mL (25%) as compared to 12 out of 34 (35%) responders (*P* value=0.466). The median change of procalcitonin from day 1 to day 3 was -0.002 (-0.018–0.003) mcg/L for the non-responder group and it was 0.005 (-0.008–0.036) mcg/L for the responder group (*P* value=0.062) ROC curve for accuracy of day in procalcitonin in predicting non-response on day 3 showed an area of 0.71 (0.553, 0.866) (*P*=0.018). Using a cut off of 0.109 µg/L, the sensitivity for day 3 non-response was 50 % and specificity was 80 %. While a cut off 0.4 µg/L yielded a sensitivity of 63% and specificity of 100% (FIGURE 1) for predicting overall need for second line rescue therapy.

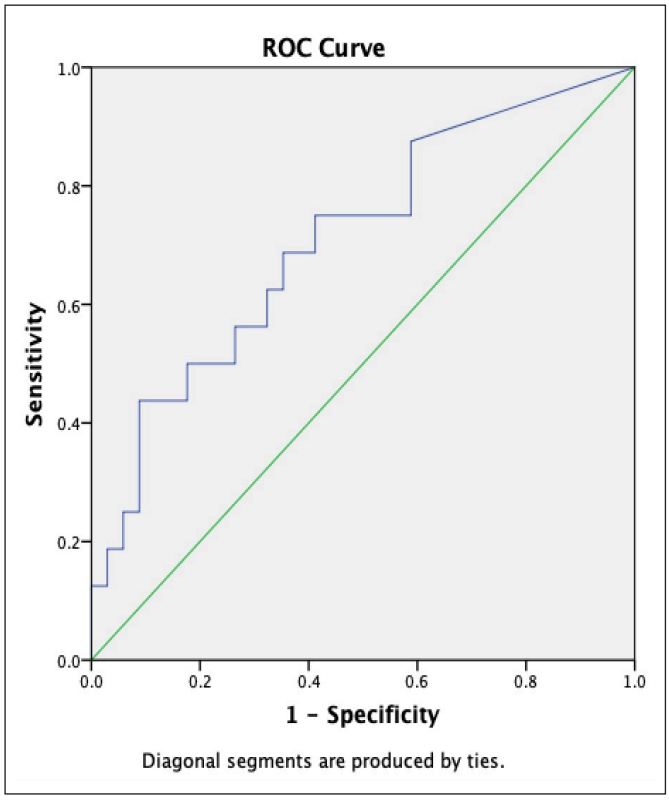

FIGURE 1. Receiver operating characteristic curve for procalcitonin levels for prediction of response as per Oxford Criteria on day 3.

Neither day 1 nor day 3 procalcitonin was significantly associated with the eventual need for second line rescue therapy by day 28 (TABLE 2). Also, the decline in serum procalcitonin did not seem to differ between the groups receiving antibiotics or placebo (TABLE 3).

TABLE 2. Serum procalcitonin levels between those responding to steroids and those requiring second line therapy.

Need for second line	Yes (n=10)	No (n=40)	*P* value
Day 1 procalcitonin (µg/L)	0.105 (0.025–0.258)	0.105 (0.025–0.258)	0.092
Day 3 procalcitonin (µg/L)	0.1045 (0.03–0.2)	0.045 (0.02–0.105)	0.181

TABLE 3. Serum procalcitonin levels between in patients on antibiotics vs placebo.

Procalcitonin	Antibiotic (n=25)	Control (n=25)	*P* value
Day 1 procalcitonin (µg/L)	0.065 (0.417)	0.026 (0.344)	0.173
Day 3 procalcitonin (µg/L)	0.07 (0.029)	0.039 (0.69)	0.815

DISCUSSION

In our evaluation of the role of procalcitonin as a biomarker in acute severe ulcerative colitis, all the patients had a value lower than the standard cut off 0.5 µg/L. The levels were significantly higher in patients who did not show any response on day 3 as per the Oxford criteria. However, in contrast to the previously reported optimal cut off of 0.1 µg/mL, we did not see a similar predictive value for this cut-off[16]. There was no difference in the baseline or day 3 procalcitonin levels between those patients who required second line rescue therapy and those who eventually responded to intravenous corticosteroids.

Ulcerative colitis is a chronic inflammatory disease and dysbiosis has been implied in the pathophysiology of the disease. Fecal microbiome analysis in patients with acute severe colitis has demonstrated a reduced overall diversity with high intra cohort variation[19]. A decrease in *Firmicutes* and increase in genera of *Gammaproteobacteria* class is noted, which is distinct from the microbiome signature of healthy controls or people with mild to moderately active UC[20]. This shift in microbiome and the increased level of TNF receptors may have lead to the procalcitonin levels which were observed. Since we had excluded patients with sepsis or those with evidence of *Clostridioides difficile* infection, we did not expect a drastic increase in procalcitonin levels. Furthermore, Aeromonas caviae was grown on stool culture of a single case (2% of entire cohort). Hence, the patients in our cohort did not seem to be infected with gram negative enteric bacteria, further explaining the relatively low levels of procalcitonin. Gut microbiome has been associated with the response to treatment in patients with ulcerative colitis. Microbiome rich in OTUs from *Clostridioides* order have been linked to a response to 5-ASA and corticosteroids[21,22]. The differences in baseline procalcitonin between patients who showed a complete or partial response on day 3 may be attributed to the differences in severity of inflammation as well as the degree of dysbiosis. However, the lack of correlation with the eventual need for second line rescue therapy highlights the importance of the trend of biomarkers rather than the absolute baseline value, when evaluating for the response to therapy. It also suggests that procalcitonin may not be the perfect biomarker for prognosticating these patients.

The only possible value of performing serum procalcitonin may be to differentiate self-limited infective colitis from a flare of inflammatory bowel disease, and may suggest the presence of other infective complications as well[23]. Wu et al. evaluated the role of procalcitonin in predicting response in patients with ASUC. They found that baseline procalcitonin level >0.1 μg/mL positively correlated with failure of corticosteroid therapy, failure of second line medical therapy and could accurately predict the need for colectomy[16]. Although the infection profile of their patients has not been mentioned, one third of the patients had received steroids previously, and a higher percentage of patients in the surgical group had previously been on immunomodulators and biologics. In comparison, none of the patients in our study had received biologicals previously and 26% had presented for the first time. Further almost 46.7 % of the patients in the previous study failed steroids which is much higher than the usually reported steroid failure rate. Thus, the baseline features may account for the difference observed.

Our study has a few limitations, including a small sample size and that we did not evaluate the gut microbiome. Also, we excluded patients with suspected sepsis or those with toxic megacolon to ensure homogeneity of patients and to ensure the analysis only in patients with disease activity rather than underlying infection.

In conclusion, the present study shows that although serum procalcitonin of patients with ASUC may accurately predict non response to steroids as per Oxford criteria, it is not an accurate biomarker to predict the need for second line rescue therapy.

Authors' contribution

Mishra S: data collection, initial draft, literature review. Ram S and Sharma AK: laboratory support and revision of manuscript. Prasad KK: histopathology and revision of manuscript. Dutta U: clinical care of patients, revision. Sharma V: conception, study design, manuscript revision. All authors approved the final version.

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Shubhra Mishra: 0000-0002-8048-9760.
Sant Ram: 0000-0001-8418-7308.
Kaushal K Prasad: 0000-0001-5864-961X.
Arun K Sharma: 0000-0002-3524-748X.
Usha Dutta: 0000-0002-9435-3557.
Vishal Sharma: 0000-0003-2472-3409.

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RESUMO – **Contexto** – A procalcitonina pode estar aumentada em colite ulcerativa ativa. Investigamos o papel da procalcitonina na previsão de resposta na colite ulcerativa aguda grave. **Métodos –** Foram inscritos pacientes consecutivos com colite ulcerativa aguda grave diagnosticados com base nos critérios de Truelove e Witts. Os níveis de procalcitonina sérica dos pacientes foram medidos consecutivamente na internação e no terceiro dia. Avaliamos o papel dos valores procalcitonina na apresentação e na avaliação da resposta no terceiro dia (critérios de Oxford) e necessidade de terapia de segunda linha (dia 28). **Resultados –** Dos 50 pacientes (23 homens, idade média: 35,98±13,8 anos), 16 não responderam (terceiro dia). Dez pacientes (20%) necessitaram de terapia de segunda linha. A procalcitonina de linha de base foi significativamente associada à resposta no terceiro dia (*P*=0,016). Não houve associação entre o primeiro dia ou o terceiro dia de procalcitonina e necessidade de terapia de resgate de segunda linha. **Conclusão –** A procalcitonina sérica não é um biomarcador eficaz para prever desfechos ou necessidade de terapia de segunda linha em colite ulcerativa aguda grave.

Palavras-chave – Doença inflamatória intestinal; colectomia; cirurgia; desfechos; colite ulcerativa.

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