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Original Article

Biochemistry Section

Role of C-Reactive Protein in Diagnosis and Prognosis of Acute Pelvic Inflammatory Disease: A Prospective Observational Study

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ABSTRACT

Introduction: Acute Pelvic Inflammatory Disease (PID) may present with a variety of clinical manifestations. Early and accurate diagnosis of acute PID is of major importance in reducing the risk of subsequent gynaecological complications inherent to this disease. C-Reactive Protein (CRP) is an acute-phase reactant that rises rapidly in response to inflammation and can be used to support the diagnosis, management and prognosis of PID.

Aim: To study the role of CRP in the diagnosis and prognosis of acute PID and to compare it with Total Leukocyte Count (TLC) and Erythrocyte Sedimentation Rate (ESR).

Materials and Methods: This prospective observational study was carried out in the Department of Obstetrics and Gynaecology, Umaid Hospital, Dr. SN Medical College, Jodhpur, Rajasthan, India, between June 2008 and May 2009. A total of 25 clinically diagnosed patients of acute PID (presenting with abdominal pain, fever, palpable adnexal mass, cervical motion tenderness, and/or unhealthy cervical discharge) were included in the study. Haematological investigations, including CRP, TLC and ESR, were performed. The patients received conservative treatment, and their clinical condition was monitored and associated with CRP, TLC and ESR values, which were repeated on the 3rd, 7th, and 21st days. The p-values were calculated using the paired t-test.

Results: The majority of patients (48%) were in the age group of 21-25 years. The mean age at presentation was 27.88±6.20 years. On admission, CRP was elevated in 96% of patients, while TLC and ESR were raised in 64% and 88% of patients, respectively. TLC levels showed a significant decrease (p-value<0.001) by the third day of treatment. Mean ESR levels increased on the third day but decreased significantly (p-value<0.001) between the third and 21st day of treatment; however, they did not return to normal even by day 21. CRP levels decreased significantly (p-value<0.001) on days 3 and 7, while the decline from day 7 to day 21 was less significant (p-value<0.01). By day 21, CRP was undetectable in all patients.

Conclusion: CRP was found to be more sensitive than TLC and ESR in supporting the clinical diagnosis of acute PID. Furthermore, compared with TLC and ESR, changes in CRP levels associated more closely with clinical improvement.

Keywords: Endometritis, Laparoscopy, Salpingitis, Sexually transmitted disease, Upper genital tract infection

INTRODUCTION

The PID is a clinical diagnosis that implies infection and inflammation of the upper genital tract. The inflammation may occur at any point along a continuum that includes endometritis, salpingitis and peritonitis [1]. Each year, over one million women are diagnosed with PID in the United States and one in seven women will experience acute PID during her lifetime [2]. Although some studies suggest an overall decline in PID diagnosis, others have reported a possible increase in its incidence [3,4]. Risk factors for PID include young age, low socio-economic status, early onset of sexual activity, multiple sexual partners, previous sexually transmitted infections, smoking and insertion of an Intrauterine Contraceptive Device (IUCD) [5-7]. PID may present in acute, subacute, or chronic forms. A variety of microorganisms can cause or contribute to acute PID. The sexually transmitted pathogens *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are implicated in about two-thirds of cases [8]. However, many PID cases test negative for Sexually Transmitted Diseases (STDs). In such cases, upper genital tract infection is thought to result from bacteria ascending from the lower reproductive tract [9-11].

Acute PID may present with a wide range of clinical manifestations, including lower abdominal and/or pelvic pain, yellow or green vaginal discharge, heavy menstrual bleeding, fever, nausea, vomiting, diarrhoea, dysmenorrhoea and dyspareunia. Some patients may also report symptoms suggestive of a Urinary Tract Infection (UTI) [9]. Early and accurate diagnosis of acute PID is crucial in reducing the risk of infertility and other gynaecological complications inherent to the disease [2]. Due to the limitations of various diagnostic tools, haematological tests have been used to support the clinical diagnosis of acute PID.

Only a few studies in the literature have compared haematological investigations in the diagnosis and prognosis of acute PID [12-14]. Furthermore, these studies report variable results; for example, the proportion of patients with acute PID who showed elevated CRP levels has been reported to range from 45-100% [15-17]. Hence, the present study was undertaken to compare CRP with TLC and ESR in the diagnosis and prognosis of acute PID.

MATERIALS AND METHODS

The present prospective observational study was conducted in the Department of Obstetrics and Gynaecology, Umaid Hospital, Dr. SN Medical College, Jodhpur (Rajasthan, India), over a period of one year, from June 2008 to May 2009. The study was conducted after obtaining ethical approval from the Institutional Ethics Committee. Informed consent was obtained from all patients prior to their participation.

Inclusion criteria: The study included 25 clinically diagnosed patients of acute PID in the age group of 21-45 years. Lower abdominal pain of less than three weeks' duration, along with any two of the following manifestations, was taken as the clinical criteria for diagnosing acute PID [18]:

Raised body temperature (>101 °F orally)

Cervical motion or adnexal tenderness on bimanual examination

Palpable adnexal mass

Unhealthy cervical discharge.

Exclusion criteria: Pregnant and lactating women, those already on antibiotics, and those with deranged liver or kidney function were excluded from the study.

Sample size: The sample size was calculated using the following formula:

$$N = \frac{Z_{1-\alpha/2}^2 P (1-P)}{d^2}$$

P= Expected proportion in the target population estimated to have particular characteristic, it is 1.5% (0.015) [18]

$Z_{1-\alpha/2}^2$ = it is standard normal variate (at 5% type I error i.e., p<0.05, it is 1.96)

d= allowable error of 5%

$$N = \frac{(1.96)^2 \times 0.015 (1-0.015)}{(0.05)^2}$$

$$= 22.70$$

Study Procedure

A detailed history was taken with special emphasis on presenting symptoms, menstrual history, obstetric history, history of IUCD insertion, history of gynaecological operations or instrumentation of the genital tract, and sexual behaviour, in order to apply the inclusion and exclusion criteria. The physical examination included general examination, per-abdomen and per-speculum evaluation. Laboratory investigations including CRP, TLC and ESR were performed at admission. A peripheral leukocyte count >10,000/mm^3, ESR >15 mm/hour, and CRP >6 mg/L were considered abnormal [18,19]. Quantitative CRP immunoturbidimetry was used for the estimation of CRP levels. Pelvic ultrasound was performed for each patient to identify uterine or adnexal pathology such as tubo-ovarian mass or fluid in the pouch of Douglas.

All patients were started on injectable antibiotics (ceftriaxone 1 g 12-hourly, gentamicin 80 mg 12-hourly and metronidazole 500 mg 12-hourly), along with analgesics and antipyretics. Intravenous fluids were given for the first 48 hours. From the fourth day onwards, oral antibiotics were prescribed, including doxycycline 100 mg twice daily and metronidazole 500 mg twice daily, for a total duration of 14 days. Patients were monitored clinically, and haematological investigations were repeated on the 3rd, 7th, and 21st days.

STATISTICAL ANALYSIS

Quantitative variables were expressed as percentages, means, and standard deviations. The paired t-test was used to compare the means of related groups, and p-values were calculated using Statistical Package for the Social Sciences (SPSS) software version 20.0.

RESULTS

The patients' ages ranged from 21 to 45 years, with the most commonly affected group being 21-25 years (48%). Sixteen patients (64%) were multiparous. Predisposing factors for acute PID were identified in five patients (20%): two patients (8%) had a history of IUCD insertion, two patients (8%) had a history of endometrial curettage, and one patient (4%) reported multiple sexual partners. At admission, lower abdominal pain was present in all patients. The most common clinical sign was adnexal tenderness, observed in 21 patients (84%) [Table/Fig-1]. A tubo-ovarian mass was detected in one patient on ultrasonography [Table/Fig-2].

CRP was elevated in 24 patients (96%), TLC in 16 patients (64%), and ESR in 22 patients (88%) [Table/Fig-3].

Demographic parameter	n (%)
Age (years)	
21-25	12 (48)
26-30	7 (28)
31-35	4 (16)
36-40	1 (4)
41-45	1 (4)
Parity	
Nulliparous	5 (20)
Primiparous	4 (16)
Multiparous	16 (64)
Presence of risk factors	
History of IUD insertion	2 (8)
History of endometrial curettage	2 (8)
Multiple sex partners	1 (4)
Symptoms	
Pain abdomen	25 (100)
Vaginal discharge	13 (52)
Fever	11 (44)
Irregular menses	10 (40)
Signs	
Adnexal tenderness	21 (84)
Purulent cervical discharge	11 (44)
Raised body temperature	11 (44)
Cervical motion tenderness	11 (44)
Adnexal mass	1 (4)

[Table/Fig-1]: Demographic profile of the patients.

Findings on ultrasound	n (%)
Uterus- normal, no adnexal mass bilaterallly	23 (92)
Uterus-normal in size and echotexture, no adnexal abnormality bilaterally except pelvic vessels congested and slight fluid in Pouch of Douglas present	1 (4)
Uterus -normal size and echotexture, a complex adnexal mass measuring 4.5×5 cm in right adnexa having internal echos, left adnexa normal	1 (4)

[Table/Fig-2]: Ultrasonographic findings of the patients.

Variable	n (%)
TLC (>10,000/mm^3)	16 (64)
ESR (>15 mm/hr)	22 (88)
CRP (>6 mg/L)	24 (96)

[Table/Fig-3]: Distribution of patients according to increased TLC, ESR and CRP on admission.

On serial testing at days 0, 3, 7, and 21, the mean leukocyte count decreased from 12.10±2.34 (×10^3 cells/mm^3) at admission to a normal value of 7.43±2.03 (×10^3 cells/mm^3) on the third day of treatment, and it remained within normal limits thereafter [Table/Fig-4]. The mean ESR at admission was 55.13±21.43 mm/hour, which increased to 60±22.87 mm/hour on the third day of treatment. Although ESR values decreased significantly from the third to the 21st day, they did not return to normal. The mean CRP level at admission was 85.72±102.35 mg/L, which decreased to 40.92±52.13 mg/L by the third day and 15±21.10 mg/L by the seventh day. By the 21st day, CRP was undetectable in all patients [Table/Fig-4].

Clinical improvement (assessed by the absence of abdominal pain, fever and adnexal tenderness) with treatment, and its comparison with different laboratory parameters, is presented in [Table/Fig-5]. Changes in CRP levels corresponded most closely with clinical improvement.

Days of treatment	Changes in leucocyte count		Changes in ESR value		Changes in CRP value	
	Mean value±SD	p-value	Mean value±SD	p-value	Mean value±SD	p-value
0	12.10±2.34		55.13±21.43		85.72±102.35	
3	7.43±2.03	<0.001	60.00±22.87	<0.001	40.92±52.13	<0.001
7	7.20±2.21	<0.001	34.86±15.98	<0.001	15±21.10	<0.001
21	7.04±2.22	<0.001	23.27±7.52	<0.001	3.72±0.79	<0.01

[Table/Fig-4]: Changes in mean leucocyte count (x103 cells/mm^3), ESR values (mm/hour) and CRP values (mg/L) after treatment.
SD: Standard deviation

Days of treatment	Number of patients								
	Pain abdomen	CMT	Purulent cervical discharge	Adnexal mass	Raised temperature	Adnexal tenderness	CRP >6 mg/L	ESR >15 mm/hr	TLC >10,000 cells/mm^3
0	25	11	11	1	11	21	24	22	16
3	21	11	11	1	0	16	23	22	0
7	14	7	5	1	0	11	14	22	0
21	0	0	1	0	0	0	0	22	0

[Table/Fig-5]: Clinical improvement with treatment and comparison with different laboratory parameters.
CMT: Cervical motion tenderness

DISCUSSION

Acute PID is a major gynaecological problem in young women. Despite advances in prophylaxis and therapy, patients with acute PID still constitute a considerable proportion of gynaecological clinic cases. In the present study, the most common age group affected was 21-25 years (48%), followed by 26-30 years (28%). Vanamala VG et al., reported that the most commonly affected age group was 26-30 years (54%), followed by 20-25 years (19.3%) [20]. Early marriage and early onset of sexual activity are important risk factors for PID, contributing to its increased incidence among younger females [5,21].

In this study, 64% of patients were multiparous, whereas Vanamala VG et al., reported that 93% of their patients were multiparous [20]. The most common clinical features in present study were abdominal pain (100%), abnormal vaginal discharge (52%), and adnexal tenderness (84%). Eggert J et al., also reported similar findings, with abdominal pain present in 98%, abnormal vaginal discharge in 45%, and adnexal tenderness in 80% of patients [15]. However, it is recognised that symptoms and signs of PID vary widely among women, making diagnosis challenging. Many women present with subtle or mild symptoms that are not easily recognised as PID, and some may develop PID without any overt symptoms [21].

Various investigations have been employed to enhance the specificity of the clinical diagnosis of acute PID, including microscopic examination of cervical discharge, sonography, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), laparoscopy, and endometrial biopsy [1,22]. Sonography is a primary imaging modality in suspected acute PID, often demonstrating thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex. CT and MRI can provide additional information, such as distinguishing tubo-ovarian abscesses from peri-appendiceal abscesses and ovarian neoplasms. However, imaging modalities have limitations: (a) lack of pathognomonic features, (b) radiation exposure with CT, and (c) limited availability of MRI [23,24].

Laparoscopy remains the most accurate method for confirming the diagnosis of acute PID, but it is invasive and both logistically and economically impractical for routine use in all suspected cases. Endometrial biopsy with histopathological evidence of endometritis is an alternative to laparoscopy; however, it is also invasive and results may be delayed by 2-3 days, limiting its clinical utility [18].

Because of the limitations of clinical, radiological and invasive investigations in diagnosing acute PID, haematological investigations have been used to support the diagnosis. The Centres for Disease Control and Prevention (CDC) has recommended ESR and CRP levels to enhance the specificity of clinical criteria and support the diagnosis of PID [11]. In the present study, TLC, ESR and CRP were compared to establish their role in the diagnosis of acute PID. Peripheral leukocyte count was elevated in 64% of patients. ESR performed better than TLC, with abnormal values noted in 88% of patients. CRP showed the highest sensitivity among the three laboratory parameters, with abnormal values detected in 96% of patients.

Previous studies have reported wide variation in these parameters. The WBC count has been reported to be elevated in fewer than 50% of patients and ESR in about 75% of patients with acute PID [18]. Similarly, CRP positivity rates have varied considerably. For example, in a retrospective study by Eggert J et al., 45% of patients had elevated CRP values [15]; Ekert LO et al., reported CRP elevation in 71% of patients [16]; while Romosan G et al., observed abnormal CRP values in 100% of patients [17].

In the present study, treatment response was assessed by monitoring the clinical condition (abdominal pain, fever and adnexal tenderness) alongside haematological investigations (TLC, ESR, and CRP) repeated on days 3, 7 and 21 after initiation of treatment. The laboratory values were compared with clinical improvement. Present study observed that TLC values decreased to normal in all patients within three days; however, this did not correlate well with clinical improvement. On day 3, 21 patients continued to experience lower abdominal pain despite normal TLC values. ESR values increased until day 3, followed by a significant decrease by day 7. However, in most patients, ESR remained elevated even on day 21, despite clinical improvement. In contrast, CRP levels decreased significantly within three days of treatment, and their trend closely paralleled the patients' clinical condition.

The prognostic value of the laboratory parameters observed in present study was comparable to that reported by Relgic M and Gorisek B [14].

Out of the three haematological parameters evaluated in this study, CRP levels were found to be superior for both diagnosing and assessing the treatment response in acute PID. Possible reasons include the fact that circulating concentrations of CRP begin to rise within six hours of the onset of an inflammatory stimulus, with the magnitude of elevation depending on the extent of tissue injury. Owing to its short half-life (approximately 18 hours), CRP levels promptly decline once the inflammatory stimulus is removed. Sequential measurements are therefore useful for monitoring disease activity [19].

In contrast, leukocytosis is often absent in non pyogenic infections [8]. Fibrinogen, the principal determinant of ESR, rises more slowly during acute infection. Because the half-life of fibrinogen is about

one week, its levels remain elevated for a longer period even after the resolution of inflammation. Furthermore, ESR values may vary with age and haemoglobin concentration [25].

Limitation(s)

The limitations of the present study was its relatively small sample size and the fact that it was conducted at a single centre, both of which may reduce the generalisability of the findings.

CONCLUSION(S)

Clinical evaluation and radiological investigations have limitations in diagnosing acute PID. Haematological parameters (CRP, TLC and ESR) are non invasive tools that can support the clinical diagnosis. The present study concluded that CRP estimation is more sensitive than TLC and ESR in this regard. Moreover, CRP was found to be more reliable than TLC and ESR for evaluating treatment efficacy in acute PID. Future studies with larger sample sizes and conducted across multiple centres are recommended to validate these findings.

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