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EVALUATION OF PROCALCITONIN FOR DIAGNOSIS OF PERITONITIS IN PATIENTS ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.

Microbiology

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ABSTRACT

Introduction- Continuous Ambulatory Peritoneal dialysis(CAPD) is the established treatment modality for patients with end-stage renal disease. Peritonitis is the most common complication noted and remains the major cause of morbidity and mortality. Early diagnosis of peritonitis would help to start the treatment and thereby reduce the complications associated with it. Culture of the effluent is the most common practice but associated with high false negative rate, therefore inflammatory markers such as erythrocyte sedimentation rate, white blood cell count, dialysate cell count, Procalcitonin and C-reactive protein(CRP) have been studied and documented.

Aim- To evaluate the usefulness of Procalcitonin for the diagnosis of peritonitis.

Material and Method- This was a prospective observational study conducted from August 2014- October 2016. During this period 61 clinically diagnosed peritonitis patients who were on CAPD were studied.

Result- Patients age ranged from 16-77 yrs ,with a mean age of 54.6 yrs. There was male 81.9% (n=50)preponderance over females 18.0%(n=11). Duration of CAPD before development of peritonitis ranged from 8 months to 36 months .All the patients were hypertensive and 49.18% (n=30) were diabetic. Out of 61 peritonitis patient samples, only 19 (31.1%) were culture positive , CRP levels were elevated in 49.1 %(n=30) while PCT levels were elevated in 70.5%(n=43). Among culture positives, 68.4%(n=13) grew gram negative organism, 15.7%(n=3) gram positive organism, 10.5%(n=2) fungi and only 1 (5.2%) grew mycobacterium tuberculosis. Escherichia.coli was the Predominant organism. After appropriate treatment 68.80%(n=42) of patient recovered, while catheter had to be removed in 22.4%(n=14) and despite of all measures 8.19%(n=5) of patient expired.

Conclusion- Procalcitonin showed promising result for the diagnosis of peritonitis.

KEYWORDS

Continuous Ambulatory Peritoneal dialysis, Procalcitonin, CRP.

INTRODUCTION:

Continuous Ambulatory Peritoneal dialysis (CAPD) is a form of home-based renal replacement therapy for patients with end-stage renal disease(ESRD).Patient's peritoneum is used as a dialysis membrane across which water and solutes (electrolytes and glucose) are exchanged between dialysis fluid and blood. CAPD has several advantages including greater ease of technique to master, greater preservation of residual renal function (RRF), better survival, and superior cost effectiveness compared to haemodialysis Despite these benefits, the outcome of CAPD patients remains poor and cardiovascular events continue to be the leading cause of death in Peritoneal Dialysis patients [1-4].

Peritonitis is the most common infection in CAPD patients and has been noted to be not only a major cause of morbidity and mortality but also the leading cause of technique failure[5]. Early diagnosis of peritonitis would be helpful, to start the therapeutic treatment and also to reduce the complications associated with it.

Diagnosis of peritonitis is confirmed when at least two of the following are present: (i) clinical features consistent with peritonitis, i.e., abdominal pain and/or cloudy dialysis effluent; (ii) dialysis effluent white cell count above 100/μL or with over 50% of polymorphonulcear leukocyte in the differential count; and (iii) identification of infective organisms from by dialysis effluent Gram stain or culture [6].

Culture of the effluent is the most common practice used for diagnosis of peritonitis but is positive, in 30-50% cases only with or without centrifugation respectively. Recovery rate of pathogens is said to increase with filtration or centrifugation of large volume of the peritoneal fluid.[7,8]

Several, conventional inflammatory markers such as erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, dialysate cell count, Procalcitonin(PCT) and C-reactive protein (CRP) have been studied and well documented in CAPD peritonitis. [5].An association between a decline in RRF in patients with Chronic Kidney Disease (CKD) and progressively increased level of systemic inflammatory burden is most marked in those receiving renal replacement therapy[9,10].

In normal conditions PCT levels remain undetectable (<0.01ng/ml), whereas in the cases of infections its levels elevate rapidly from the second hour of infection. Further, CRP an acute phase protein and a marker for inflammation is also found to be associated with high mortality in patients on peritoneal dialysis[9-12].

Therefore, the present study was aimed to determine the levels of CRP and PCT in the clinically diagnosed peritonitis patients who were on CAPD and also to evaluate the usefulness of PCT in comparison to CRP and culture.

MATERIALS AND METHODS:

This was a prospective observational study conducted from August 2014- October 2016. During this period 61 clinically confirmed peritonitis patients who were on CAPD were studied. Two ml of

Blood sample for estimation of CRP and Procalcitonin, and 50 ml of CAPD fluid was collected for bacterial, mycobacterial and fungal culture.

Clinically confirmed peritonitis defined as patient present with cloudy lysate bag/abdominal discomfort with PD cell count >100/ul (>50% polymorphonuclear cells).

Sample collection and processing:
Serum was separated from blood sample and stored at 2-8°C until further processing. The peritoneal Dialysis affluent was processed for bacterial, mycobacterial and fungal microscopy and culture as per guide lines (International society of Peritoneal Dialysis) CRP- was tested by using Immunopak C-reactive Protein kit supplied by Recon Diagnostics P. Ltd., Gorwa, Vadodara, India.

PCT- levels were determined quantitatively by fluorescence immunoassay (QDX instacheck TM PC manufactured by Boditech Med Incorporated, Gang-won-do, Korea). The test was performed as per the instructions provided by the kit and results were automatically calculated by the reader. It detects Procalcitonin ranging from 0.25 to100ng/ml.

Statistical analysis
The data was analysed using IBM SPSS for Windows 16.0. All data were expressed as mean ± SD for normal distribution and median or range values were used for skewed data. Chi-square test was used in univariate analysis. A p value 0.05 is considered for statistical significance.

RESULTS:
During the study period, a total of 61clinically confirmed peritonitis patients , who were on CAPD studied. Patients age ranged from 16-77 yrs ,with a mean age of 54.6 yrs. There was male 81.9% (n=50) preponderance over females 18.0%(n=11). Duration of CAPD before development of peritonitis ranged from 8 months to 36 months .All the patients were hypertensive and 49.18% (n=30) were diabetic.

Out of sixty one peritonitis patient samples, only 19 (31.1%) were culture positive , CRP levels were elevated in 49.1 %(n=30) while PCT levels were elevated in 70.5%(n=43).[figure-1]

Among culture positives, 68.4%(n=13) grew gram negative organism, 15.7%(n=3) gram positive organism, 10.5%(n=2) fungi and only 1 (5.2%) grew *mycobacterium tuberculosis*.[figure-1] Among GNBs most predominant isolate was *Escherichia.coli* (E.coli) 38.4%(n=5) followed by *Pseudomonas aeruginosa* 30.76% (n=4), *Klebsiella pneumoniae* 15.38% (n=2), and *non fermentative gram negative bacilli* (NFGNB) and *Enterobacter* one each(7.69 %) in descending order. Among Gram positive organisms, *Staphylococcus aureus, Coagulase Negative Staphylococcus,* and Beta *hemolytic streptococcus*(BHS) were isolated, one each(n=1). Among fungal isolates, *candida non albicans* and *Fusarium* were isolated, one each(n=1).[figure-2]

Treatment was started immediately after sending the sample, as per ISPD guidelines, and of all patients, 68.80%(n=42) of patient recovered, while catheter had to be removed in 22.4%(n=14) and despite of all measures 8.19%(n=5) of patient expired.[table-1]

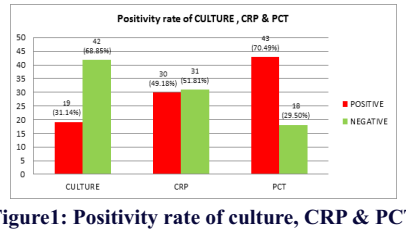

Figure1: Positivity rate of culture, CRP & PCT.

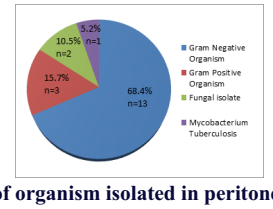

Figure2:Type of organism isolated in peritoneal fluid culture.

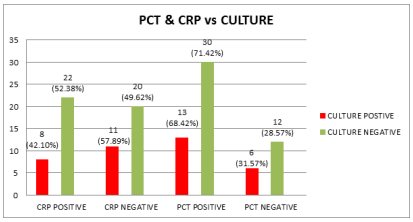

Figure 3 -CRP & PCT positivity in Culture Positive and Culture Negative Samples.

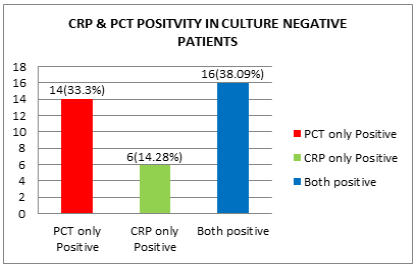

Figure 4-CRP &PCT positivity in culture negative samples.

Table 1.- shows outcome of the peritonitis patients.(n=61)

	Recovered	Catheter Removal	Expired
Diabetic (n=30)	21	5	4
Non-diabetic (n=31)	21	9	1
Total (n=61)	Total (n=42)	Total (n=14)	Total (n=5)

DISCUSSION
Peritonitis in CAPD patients is a common problem which is associated with mortality and morbidity and several other complications. Diagnosis of peritonitis in patients on continuous ambulatory peritonitis is of utmost importance so as to initiate appropriate treatment at the earliest possible time to decrease morbidity and mortality.

Though culture is the gold standard for diagnosis of infective peritonitis, it is negative in 28-70% of cases [11,13-16]. because of this reason, several inflammatory markers are evaluated to assess the diagnosis of peritonitis.

Although, various studies are available in literature which have assessed the value of procalcitonin to differentiate between infectious and non infectious etiology causing sepsis, there are very few studies available on the significance of procalcitonin levels in diagnosing peritonitis in CAPD patients.[17,18] Moreover, unlike other inflammatory markers, PCT level does not respond to viral infection or sterile inflammation. Thus, this study was conducted to assess the usefulness of PCT for diagnosis of peritonitis in CAPD patients in comparison to CRP.

In the present study 61 clinically diagnosed peritonitis cases were studied and showed a very high culture negative rate 68.8%(n=42) which is far greater than that suggested in ISPD guidelines(>20%). High culture negativity rate has been observed in several studies with conventional culture techniques [13-15]. Reason for culture negative peritonitis can be attributed to non adherence to ISPD recommendations with regard to culture specimen collection and use of substandard media for culture especially in the public sector hospitals and sub-optimal microbiological techniques, same may be attributed to our study also.

Unlike western literature ,in the present study gram negative organisms were predominant with *Escherichia. coli* being the most common isolate. Similar results has been reported from many other studies in India [13-15,19].

Proper treatment is crucial for favourable outcome of PD related peritonitis. Microbiological culture is the gold standard for diagnosis but suffers from delayed reporting and high false negative rates. Therefore, inflammatory markers like CRP and Procalcitonin were

evaluated for the diagnosis of peritonitis that can shorten the turnaround time of laboratory reports.

Various studies showed that C-reactive protein (CRP) correlates with the disease progression and out comes of PD-related peritonitis, however, the increase of CRP could be related to non infectious causes[20-22].Meanwhile, recent studies showed that level of serum procalcitonin (PCT), the precursor of as calcitonin, correlates with infection and showed good sensitivity and specificity for the early diagnosis of systemic bacterial infection in PD patients [23-26].

Present study showed that serum PCT levels were elevated in 70.49%(n=43) of clinically confirmed patient samples while CRP levels and culture positivity were seen in 49.18%(n=30) and 31.14%(n=19) of patient samples respectively.[Figure1] Study depicts that serum procalcitonin was good indicator for the detection of peritonitis and the detection rate is statistically significant when compared with that of CRP and culture.

On further analysis of the culture positive samples , it was observed that PCT was positive in 68.42% (n=13) and CRP levels were raised in 42.10% (n=8) of the samples. Statistically significant difference was seen in the positivity rate of PCT as compared to CRP among culture positive samples.[Figure 3] Study also showed that the Procalcitonin positivity was more in bacterial culture positive samples ,[data not shown] which is in concordance with the reported studies.

It was evident from the study that among the culture negative peritonitis samples, PCT was positive in 71.42%(n=30) and CRP was raised in 52.38%(n=22) of samples. PCT alone was positive in 33.3%(n=14) while CRP alone was positive in 14.28%(n=6) of the culture negative cases.[figure 4]. On the basis of our results ,we recommend that in addition to the defined criteria for diagnosis of peritonitis, there is need to include both PCT and CRP estimation as supporting evidence in re-enforcing the diagnosis of peritonitis as each technique may miss significant number of cases due to antibiotic intake or any other reason.

In the present study no difference was seen in the development of peritonitis between the diabetics and the non diabetic patients undergoing CAPD. [Table1] Role of diabetes in the development of peritonitis in CAPD patients is still debatable as studies favouring [27-29] as well as refuting it [30,31] are available in literature. We also found that both inflammatory markers(CRP &PCT) were elevated in patients with diabetics, but the rate of elevation was higher in non diabetics. Still to arrive at a conclusion a large cohort of diabetic patients and non diabetic patients undergoing CAPD have to be tested.
All the patients were treated, as per ISPD guidelines and the treatment was modified according to the culture and sensitivity report, among them 68.80%(n=42) of patients recovered, while catheter was removed in 22.4%(n=14) and 8.19%(n=5) of patients expired. There was no difference in the recovery rate between diabetic and non-diabetic but the mortality rate was significantly higher among diabetic group.[Table-1]

There is no statistically significant co-relation between level of PCT,CRP and the final out- come as patients with high level of CRP and PCT recovered well with the proper treatment but it has been noted that in all the expired cases, PCT was positive while CRP was positive only in three cases but with the higher level >24mg/dl, it has been reported in many studies that the high CRP levels indicates poor outcome[20,32].

CONCLUSION

PCT appears to be promising marker for diagnosis of peritonitis as compared to CRP but needs to be further evaluated with large sample size. Results of our study suggest that in addition to culture, estimation of more number of biomarkers such CRP and PCT would help in confirmation of peritonitis diagnosis in larger number of clinically suspected cases and initiation of timely appropriate therapy.

Limitations-It is a small size study and levels of inflammatory markers were not estimated at different time intervals of treatment which would provide valuable information about its role as a prognostic marker in patients undergoing CAPD.

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