ASSESSING AND COMPARING PERITONITIS DETECTION TECHNIQUES ON PATIENTS ON PERITONEAL DIALYSIS IN A TERTIARY CARE SETTING OF LAHORE, PAKISTAN

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ABSTRACT: *Peritonitis is considered as one of the foremost major complication of peritoneal dialysis (PD). Several studies have explored different techniques to rapidly diagnose peritonitis. Considering limited literature in this context from the region, this study was designed to determine the frequency of peritonitis and to assess and compare the detection role of different techniques in the diagnosis of bacterial peritonitis during first 48 hours in patients undergoing acute peritoneal dialysis in Lahore, Pakistan. It was a cross-sectional study conducted in Nephrology Department, Sheikh Zayed Hospital, Lahore over a period of six months. Sample of 400 patients was taken. Initial evaluation and biochemical profile was done before starting PD, All episodes of positive culture, presence of clinical peritonitis and urine dipstick (leucocyte esterase reagent) were detected and compared with culture using ROC curve and McNemar test at 24 hours and 48 hours. The pre dialysis biochemical profile of majority of the patients was mostly found deranged. Study found 156 out of 194 cultures positive where clinically peritonitis was not present. In comparison of sensitivity, specificity, ROC curve and McNemar test at 24 hours and 48 hours, urine dipstick was found to be relatively better option. Determination of culture may be reserved for confirmation of clinically suspected peritonitis but study findings suggests that urine dipstick being relatively more cost effective and convenient to practice may be used as an alternative or complementary option depending upon the available resources to help in the diagnosis of peritonitis.*

Keywords: Peritonitis, Peritoneal dialysis, Diagnosis, Leukocyte esterase.

1. INTRODUCTION:

Acute peritoneal dialysis (APD) is being used as a short-term therapy for patients presenting with acute renal insufficiency [1, 2], while for long-term treatment of end stage renal disease, chronic ambulatory peritoneal dialysis (CAPD) is used [3]. Peritonitis is considered as a foremost complication in both modalities of peritoneal dialysis (PD) [4, 5]. The peritonitis rate was found to be 36.45% in Thailand in patients undergoing acute peritoneal dialysis [6]. Dialysate interferes with peritoneal immune defenses. The acidic pH, lactate content, and hypertonicity of dialysate are non-physiologic and impair peritoneal immune function. The dilution effect of dialysate also contributes to diminished host defenses. Contamination at the time of an exchange, usually but not invariably resulting in coagulase-negative staphylococcal peritonitis, remains a leading cause of peritonitis [7]. International Society of peritoneal dialysis (ISPD) guidelines highlights the importance of peritonitis prevention and recommend that each PD program to monitor infection rates at least on a yearly basis [3].

The diagnosis of peritonitis depends upon clinical evaluation of the patient and examination of the dialysate. Peritonitis is usually present when the effluent is cloudy and or there is abdominal pain. The examination of peritoneal dialysate fluid (PDF) as per ISPD guidelines [3] include the determination of total leukocyte count, (white blood cell count of 100 cells/μL with more than 50 % polymorphonuclear cell.) [8], and peritoneal fluid cultures for the isolation and identification of microorganisms. It has been recommended that treatment of peritonitis should be initiated before the result of the dialysate cell count is available [3].

Initial and effective peritonitis treatment prevents the progress of fibrosis and adhesions and reserves the peritoneum. Uncontrolled broad spectrum antibiotics use leads to undesirable outcomes such as decrease in residual renal function and ototoxicity [9]. In the acute stages peritonitis carries a significant resource implication in terms of staff time, laboratory services, drug costs and potential need for prolonged admission [10]. Efficient diagnosis of peritonitis can permit sooner start of adequate antibiotics with possible benefit and may reduce need for hospitalization. Diagnosis could occur at point of care and eliminate confusion and allow early treatment [11]. Antibiotics are preferred empirical first line therapy to combat most frequent causative organisms [12].

A more rapid test that could be performed at the point of care would be useful if it were specific and sensitive. The urine dipstick strips are designed to give a semi quantitative indication of the level of the leucocytes present in urine based on the color of the reacted indicator pad [13]. Peritoneal leucocyte esterase is elevated and associated with increased neutrophil counts in PDF [14]. Reagent strips, traditionally used for prompt diagnosis of urinary tract infections [15-17], & urinary tract infection in pregnancy [18, 19] are now being applied to the diagnosis of other biological fluid infections such as meningitis, pleural empyema [20], spontaneous bacterial peritonitis [21-23] and peritonitis in patients on CAPD [24]. Role of urine dipstick in detecting asymptomatic bacteriuria has been questioned [25] and its role in early detection of peritonitis in patients undergoing APD needs to be further evaluated. Considering limited literature in this context from the region, this study was designed to determine the frequency of peritonitis and to assess and compare the

detection role of different techniques in the diagnosis of bacterial peritonitis during first 48 hours in patients undergoing acute peritoneal dialysis in Lahore, Pakistan.

2. MATERIALS AND METHODS:

It was a cross-sectional study conducted in Nephrology Department, Sheikh Zayed Hospital, Lahore over a period of six months. A sample of 400 was taken to achieve 85% power to detect a difference of 0.05 between the area under the ROC curve (AUC) under the null hypothesis using a two-sided z-test at 95% confidence level [26]. All patients started on Acute Peritoneal Dialysis in Sheikh Zayed Hospital, Nephrology Department were eligible. Patients receiving antibiotic therapy during previous 48 hours were excluded. After obtaining consent from each patient a proforma was used. Information was collected for primary diagnosis, signs & symptoms suggestive of peritonitis, lab investigations and dialysate exchange details. The PDF samples were analyzed at 24 Hrs. & 48 hours using urine diagnostic strip at the point of care. Urine dipstick used was "Combur 10 Test M" by Roche Will to collect a sample of peritoneal dialysate effluent in a clean container. Samples were taken and assessed by color of the indicator pad to the color chart on the bottle and grades neutrophil count as Negative; Trace Grade 1, (10-25 leucocytes / µL); Small Grade 2, (75 leucocytes / µL); or Large Grade 3, (500 leucocytes /µL.) Readings of Trace or above were regarded as significant and suggestive of peritonitis.

For culture and sensitivity peritoneal dialysis effluent was obtained aseptically by cleansing the port of the dialysate bag. 10 ml peritoneal dialysis effluent was collected in blood cultures bottle and sent immediately to laboratory. Peritoneal dialysis effluent was also obtained by removing the fluid into a heparin anticoagulant tube and sent immediately to laboratory for WBC count including differential. Data was entered and analyzed in SPSS for windows software (version 20). Descriptive results were explored. All episodes of positive culture were detected and results correlated with leucocyte count in PDF, presence of clinical peritonitis and urine dipstick (leucocyte esterase reagent) using ROC curve and McNemar test at 24 hours and 48 hours.

3. RESULTS & DISCUSSION:

A toal of 400 acute peritoneal dialysis sessions were monitored during a six month period for early detection of bacterial peritonitis and frequency of peritonitis was evaluated at the department of Nephrology, Shaikh Zayed Hospital, Lahore. The mean age of the study population was 49.6 years ± 15.9. There were 57% male and 43% female patients. Most of the patients, 72% were admitted through accident and emergency department while 28% patients got admitted throughout patient department. As far as major cause of renal disease was concerned the diabetic nephropathy was the most common cause with frequency, followed by hypertension, and chronic glomerulonephritis as shown in Table 1.

Table1: Descriptive Statistics

n = 400		Gender					
		Female		Male		Total	
		n	%	n	%	n	%
Age in Years	≤30	18	10.5%	43	18.9%	61	15.3%
	31-50	68	39.5%	66	28.9%	134	33.5%
	51-65	58	33.7%	89	39.0%	147	36.8%
	>65	28	16.3%	30	13.2%	58	14.5%
Mode of admission	Emergency	126	73.3%	162	71.1%	288	72.0%
	OPD	46	26.7%	66	28.9%	112	28.0%
Diagnosis	DM	88	51.2%	122	53.5%	210	52.5%
	HTN	42	24.4%	28	12.3%	70	17.5%
	Chronic GN	17	9.9%	48	21.1%	65	16.3%
	Other/Unknown	25	14.5%	30	13.2%	55	13.8%
Receiving antibiotics	No	59	34.3%	84	36.8%	143	35.8%
	Yes	113	65.7%	144	63.2%	257	64.3%

The pre dialysis biochemical profile of majority of the patients was mostly found deranged as elaborated in Table 2.

Table 2: Pre-Dialysis Laboratory Values

Lab tests	n	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
Hb	400	8.415	1.8980	.0949	8.228	8.602
TLC	400	9862.62	4995.400	249.770	9371.59	10353.65
Neutrophils	400	80.36	9.005	.450	79.47	81.24
Serum Creatinine	400	14.924	6.6981	.3349	14.266	15.583
BUN mg/dl	400	112.42	45.459	2.273	107.95	116.89
Serum Calcium	400	7.494	1.1339	.0567	7.383	7.606
Serum Phosphorus	400	9.553	2.7438	.1372	9.284	9.823
Serum Albumin	400	2.740	.5779	.0289	2.684	2.797
Serum Potassium	400	4.910	1.1545	.0577	4.797	5.024

Results of different peritonitis detecting techniques at 24 hours and 48 hours are shown in table 3.

Table 3: Peritonitis detection tests

		At 24 Hours		At 48 Hours	
		n	%	n	%
Culture	Negative	206	51.5%	242	60.5%
	Positive	194	48.5%	158	39.5%
TLC	Negative	387	96.8%	370	92.5%
	Positive	13	3.3%	30	7.5%
Clinical Peritonitis	Negative	362	90.5%	266	66.5%
	Positive	38	9.5%	134	33.5%
Dipstick	Negative	231	57.8%	243	60.8%
	Positive	169	42.3%	157	39.3%

Comparison of other detecting techniques with culture at 24 hours and 48 hours are shown in table 4.

Table 4: Comparison of detecting techniques

With Culture		True +ve	True -ve	False +ve	False -ve	Sensitivity %	Specificity %	P-Value[a]
At 24 Hours	TLC	5	198	8	189	2.6	96.1	0.000
	Clinical Peritonitis	32	200	6	162	16.5	97.1	0.000
	Dipstick	107	144	62	86	55.2	69.9	0.049
At 48 Hours	TLC	27	239	3	131	17.1	98.8	0.000
	Clinical Peritonitis	118	226	16	40	74.7	93.4	0.002
	Dipstick	137	222	20	21	86.7	91.7	0.999

[a] P-Values are based on McNemar test

ROC curve of TLC, Clinical peritonitis and Dipstick against Culture at 24 hours and 48 hours are shown in figure 1.

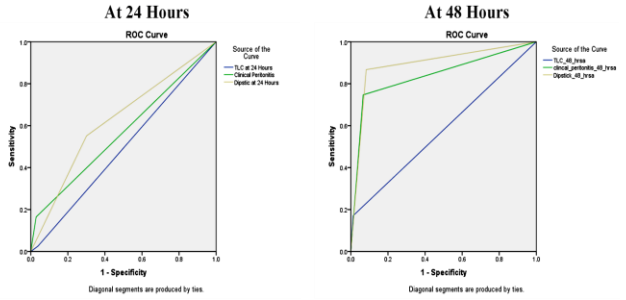

Figure 1 - ROC curve of TLC, Clinical peritonitis and Dipstick against Culture

4. DISCUSSION

Peritonitis is considered as the foremost complication of peritoneal dialysis. Though less than 4% of peritonitis incidents end to death, peritonitis is a "contributing factor" to death in 16% of deaths on PD and around 18% of the infection-related mortality in PD patients is the result of peritonitis. [15]. Initial diagnosis and suitable treatment are vital to avoid and prevent complications related to peritonitis. Treatment of PD peritonitis is conventionally started on the base of clinical signs, symptoms, and light microscopy of dialysate effluent [27]. Additionally, prolonged and severe peritonitis can cause failure of peritoneal membrane and possibly the most usual cause of technique failure in PD is peritonitis [15].

The patients who underwent acute peritoneal dialysis at Shaikh Zayed Hospital were mostly uremic having a mean serum creatinine of 14.9 mg/dl. It was difficult to distinguish whether nausea, vomiting and abdominal pain are due to uremic gastritis or due to peritonitis. In addition, due to uremic encephalopathy it was difficult to elicit signs and symptoms. These patients had also comorbid problems like pneumonia, diabetic foot and UTI that could have been the cause of fever in these patients. Yet, due to baseline hypothermia (revealed in 50% of patients on hemodialysis with subnormal predialysis body temperature) and commonly coexisting malnutrition, fever may not be observed in some dialysis patients with severe infections.

In our study frequency of clinical peritonitis at 24 hours was 9.5 % and it rose to 33.5% at 48 hours, which is comparable to study done by Dandecha et al. In a study done by Dandecha et al, for determining frequency of peritonitis in acute peritoneal dialysis in Thailand, the overall peritonitis rate was 36.45 percent [7]. The peritonitis rate rose following the duration of dialysis from 11 per cent on the first day to 21 per cent on the second day. In Korea a study on pediatric population in they found peritonitis in 78.3% of patients in patients undergoing acute PD [28].

Peritonitis diagnosis in symptomatic patients with cloudy dialysate is less problematic. Exclusion of peritonitis with signs and symptoms, but visually clear dialysate, or with suspicious looking dialysate with less or no signs and symptoms, is relatively more challenging and mostly diagnosis is confirmed by positive bacterial culture in study site and presumably in similar settings. Exploration of specific causative organisms permits antibiotic remedy to be improved and possibly lead to better outcome. Nevertheless, culture-negative peritonitis or failure to culture organisms is also common. Reported gram staining sensitivities in dialysate effluent vary between 9% - 80% and are, consequently, not extensively used for the initial diagnosis of peritonitis. The total leucocyte and neutrophil count is not always available everywhere or cannot be done in an emergency basis [29]. Peritoneal effluent cloudiness is not an precise indicator of leukocytes presence. Additionally, it is relatively subjective and there may be examples where the cloudiness is tough to interpret. Farmer et al, found peritoneal dialysate as cloudy in 6% of sample without any indication of peritonitis. It was also assumed to be because of chylous ascites but in same study despite the presence of peritonitis, another 16% were observed with clear peritoneal effluents [27].

The dwell time for CAPD patients before taking samples is minimum of two hours. This is in stark contrast a limitation to this study where initially in first 24 hours no dwell time was given and dwell time was only 15- 30 minutes after 24 hours. In a study done by Steen et al on leucocytes in peritoneal dialysis effluent the authors found that the leukocyte concentration decreases rapidly at 25°C to 75% and 70% of the initial value after 4 and 6 hours respectively. White blood cells adhering to glass and plastic surfaces are not considered stable in both urine and PD fluid containers [30]. In our study the samples were sent to laboratory where they were analyzed during 4-6 hours. This could also have contributed to the low cell count.

Leucocyte esterase reagent (LER) strips, established primarily to test for polymorphonucleocyts in urine, have also found to be useful in spotting polymorphonucleocyts in other body fluids such as ascetic, pleural, and cerebrospinal fluids. In studies though mostly conducted in developed countries, it was found to reduce the diagnosis time. The sensitivity of the dipstick to diagnose meningitis was found to be 97% [31]. The sensitivity of the dipstick to diagnosis spontaneous bacterial peritonitis (SBP) at different cut-off has been reported between 71% - 86% [21]. Leukocyte esterase reagent strips were also used to detect peritonitis in patients given treatment with continuous ambulatory peritoneal dialysis and intermittent peritoneal dialysis [15, 32, 33]. Nonetheless, this test is not locally available and is relatively expensive than urinalysis dip sticks and. Moreover, leukocyte esterase reagents have not been evaluated for diagnosing peritonitis in patients undertaking acute peritoneal dialysis. This study explored the value of leucocyte esterase in early detection of bacterial peritonitis against culture findings.

In a study conducted by Williams et al [34] on patients undergoing CAPD there was a latent interval of 72 hours or less between the presence of organisms in the dialysate and the clinical onset of peritonitis. Asymptomatic positive cultures (APC) were found in 60% of the culture positive cases. In the same study they found no relationship between frequency of APC's and the frequency of peritonitis; also they found no direct relationship between APC's on consecutive days and onset of peritonitis. Although treatment of APC's may reduce the incidence of peritonitis, it would have resulted in gross overuse of antibiotics in our patients. They concluded that culture of random specimens of dialysate from

asymptomatic patients is unlikely to give any useful clinical information as most asymptomatic positive cultures do not progress to peritonitis. In our study 156 out of 194 cultures were positive where clinically peritonitis was not present.

The clinical diagnosis of peritonitis in the setting of peritoneal dialysis is not difficult to establish. Infected patients present with fever, abdominal pain, abdominal tenderness on examination and usually have a cloudy dialysate drainage. This study compares different detecting tests for peritonitis. Although aerobic cultures of dialysate are essential to confirm the diagnosis of infective peritonitis and guide therapy, they do not provide a very rapid diagnosis. Determination of culture may be reserved for confirmation of clinically suspected peritonitis but study findings suggests that urine dipstick being relatively more cost effective and convenient to practice may be used as an alternative or complementary option depending upon the available resources to help in the diagnosis of peritonitis.

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