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TIME TO ADD PROCALCITONIN AS AN ADJUNCT BIOMARKER IN DIAGNOSING BURN SEPSIS: A TERTIARY LEVEL CARE EXPERIENCE

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ABSTRACT The most common cause for mortality in burns worldwide is sepsis. American Burn association guidelines 2007 are followed till date. But the confirmation of the sepsis requires tissue/blood culture which takes a minimum of 48-72 hours. Adding Procalcitonin as an adjunct biomarker to the sepsis criteria enhances the predictability of sepsis. This prospective study has been carried first time with the help of Procalcitonin. The prospective study was performed between October 2019 to October 2021 in the department of burns and plastic surgery wherein we evaluated serum procalcitonin of 52 patients with (30 %to 60%) Total Body Surface Area burns within 24 hour of admission and at the time of burn sepsis suspicion as per American burn Association2007 guidelines .The Positive blood/tissue culture was taken as the confirmatory evidence of sepsis. Patients were divided in two groups, sepsis (Group A) and non sepsis (Group B). All the parameters for sepsis as per ABA guidelines were serially noted . The Sensitivity and specificity of the test was 89.29 % and 58.33 % respectively. 2.1 ng/ml was taken as the cut off value for diagnosing sepsis in burn patient with an area under the curve of 0.78 at 95% confidence interval. Elevated Procalcitonin concentrations correspond to the documented sepsis in 30 -60 % of burns which enhances the Predictability of diagnosing burn sepsis .Hence we recommend to add procalcitonin as an adjunct biomarker to diagnose sepsis in burn patients.

KEYWORDS : Procalcitonin, sepsis

Introduction

Sepsis is a syndrome of various physiologic and biochemical abnormalities. Patients with large burns experience severe physiologic derangement including a sustained systemic inflammatory response, hyper metabolism and immunosuppression rendering the diagnosis of sepsis difficult in this patient population[1].The parameters which change are an increase in the patient's respiratory rate, temperature , heart rate and high glucose levels , which are also used as predictors for SIRS and sepsis. Hence traditional criteria for SIRS and sepsis are unreliable in most burn patients . The burn sepsis criteria given by ABA[2]in 2007 which is being followed worldwide till date .The new Sepsis 3 guidelines[3] are based on use of SOFA but these guidelines have not been applied in burn population . The clinical parameters of sepsis in burns as per ABA guidelines 2007 needs a microbiological culture to confirm sepsis. The emergence of PCT (Procalcitonin) as a trustworthy biomarker among the various inflammatory biomarkers of sepsis has been described in literature[4]. PCT is a 116 amino acid residue, that under normal homeostasis synthesized by thyroid C cells[5] . Proinflammatory cytokines and endotoxins synthesisize PCT from extrathyroidal tissue also. Healthy people have very low levels of PCT but markedly increased levels up to 1000 fold within 2-4 hour of sepsis onset. There are various studies done so far on the role of PCT in burn sepsis .Our study aims to find the PCT rise in different types of burn and Sensitivity and specificity of PCT in burn sepsis in North Indian population.

Materials & Methods:

The prospective observational study was performed between October 2019 to October 2021 in the department of burns and plastic surgery. After approval of the Institutional ethical committee, the consent form was prepared and signed by all the subjects. 52 patients with 30 to 60 % of Total Body Surface Area (TBSA) burns (thermal(30) ,scald (11)and electric flash (11) burn) were included in the study .Patients with electric contact burn ,chemical burns and burns less than 30 % and more than 60% TBSA burns were excluded from the study. Patients having trauma and history of any previous chronic disorder were not included in the study Those patients who came out to be Covid 19 positive during the hospital course were also excluded from study. All patients were resuscitated and treated as per Burn Protocol.PCT samples were collected within 24 hour of admission of burn for a baseline value .Patients were allotted monitored beds and the clinical parameters were noted down at the time of admission .

As per ABA 2007 guidelines for sepsis, temperature, Heart rate and respiratory rate were measured every 4 hourly. The complete blood count and sugar levels were sent alternate day .Progress of enteral feeding was also noted .Sepsis was suspected whenever patient showed three or more of the above criteria and PCT samples were sent at the same time. Tissue and blood culture were also sent at that time and patients were put on antibiotics as per institutional antibiogram.

Positive blood/ tissue culture confirmed the sepsis and was taken as the reference standard to divide the patients in to two groups of sepsis(Group A) and non sepsis (Group B) .Few patients had multiple episodes of sepsis in group B during hospital stay and hence samples of PCT were taken more than twice in those patients .Some patients responded to the antibiotics with no growth in blood or tissue culture .These patients were not included in the study .The nonsepsis group (Group B) comprised of the PCT samples of the patients who did not show the features of sepsis as per ABA criteria and the estimation of PCT was done with in 24 hrs of admission.

All the clinical parameters as mentioned above were documented in the record book along with the PCT samples .Figure 1 demonstrates the recording of various parameter in a sample patient .Sepsis group(Group A) comprised of those patients which went in to sepsis and PCT was collected at the time of suspicion of sepsis. So the two groups of sepsis (Group A) and Non sepsis (Group B) were categorized.

Whole blood in EDTA vial was taken for evaluating PCT and measured using immunoanalyzer (Radiometer AQT90 FLEX[6]) .It works on the principle of immunoassay sandwich method and florescent detection .The result was obtained in 20 minutes. The analytical sensitivity (limit of detection) for whole blood was 0.072ng/ml and the 95th percentile was determined to be < 0.12 ng/ml for the whole blood.

The variables were analysed in two groups of sepsis (Group A) and non sepsis (Group B) for mean, median and standard deviation. Receiver operating characteristic[7] (ROC) curve was prepared and the positive predictive value and likelihood ratio were also calculated. SPSS 20.0 software (IBM) was used for analysis.

Results

52 patients with different types of burns ; flame ,scald and electric flash burns were included in our study in which 30 patients were males and 22 females with a mean age of 25 yrs (1-70 yrs).The mean TBSA percentage in two groups were calculated with sepsis group having an average of 50.5 % and non sepsis group having an average of 40%. A total of 84 samples of PCT were analysed .On analysing the Median PCT value in the two groups was 8.50 ng/ml (Group A) and 1.85 ng/ml (Group B) respectively .Out of 52 patients 28 patients had sepsis and 24 patients did not go in sepsis .9 of the 28 patients developed

multiorgan failure and could not be revived .The blood culture report had Pseudomonas in 16 (57%) , klebsiella in 5 (17%) ,Proteus in 3(10%) ,Acinetobacter in 3 (10%) and staphylococcus in 1 (3%) patient. The treatment resulted in survival of nineteen patients. There was one mortality due to inhalational injury In Group B .

The ROC curve (Figure 2)was utilized for obtaining the predictive ability with an area under curve of 0.78 at 95 % confidence interval (upper bound 0.914, lower bound 0.645) which lies above the diagonal line. Each value of PCT has been charted on ROC curve .The cut off value was decided by the superior most combination of sensitivity and specificity. The cut off value of PCT was 2.1 ng/ml at the sensitivity of 89.29 % and specificity of 58.33%. The distribution of PCT values in both the groups are shown in table 1. The characteristics of diagnostic performance of PCT are highlighted in Table 2.

Discussion

Various criteria's to diagnose sepsis as per literature are ABA[2] guidelines for burn sepsis given in 2007 , Mann –Salinas [8]et al guidelines given in 2013 and the most recent ones are the Third[3] international consensus definition of sepsis and septic shock (sepsis - 3) guidelines given in 2016. But as stated by yan [9] et al in 2016 none of the criterion alone accurately diagnoses sepsis in the burn population. The basis for sepsis -3 guidelines is SOFA scoring and ABA guidelines 2007 are based on clinical signs.

ABA guidelines 2007 are followed till date world over for diagnosing burn sepsis but it needs microbial report of tissue/blood culture which takes at least 48-72 hours to confirm the diagnosis of sepsis. There has been extensive research by the burn specialists to add another criterion to the existing ABA guidelines 2007 to increase its predictibity and accuracy in diagnosing sepsis. CRP levels, Serum Ferritin, pro-adrenomedullin[10] and PCT are the known biomarkers being studied across the globe to add to the burn sepsis criteria. The high reliability ,ease of measurement and high specificity and sensitivity differentiates an T ideal parameter/biomarker[4] for early sepsis diagnosis. Some of the characteristics suggesting PCT as an ideal biomarker are its serum levels which increase 6-12 hours[5] following initial bacterial infections and rise steadily 2-4 hours following the onset of sepsis. 20-24 hours is the half –life of PCT ; also when a proper antibiotic therapy is given, PCT levels decrease accordingly by 50% in 24 hours. .Our study reveals that PCT has a high sensitivity and specificity to diagnose sepsis in burns .The quick result enhances the predictability of sepsis and spares the time lost in obtaining the culture report. Hence a burn specialist can take the necessary steps including antibiotic up gradation with early diagnosis of sepsis.

[4]Cabral et al has showed that procalcitonin is the best biomarker studied for an early diagnosis of sepsis.PCT was the biomarker with the largest Area under Curve (0.71) in his study. This analysis matches our study in which predictive ability of PCT is determined using ROC curve and AUC is 0.78 at 95% confidence interval .Though study by [11]seone et al shows that PCT is not a precise indicator of sepsis, the study on large number of patients and more number of PCT analysis by cabral[4,12] /levartina[13] /yan[9] reveals PCT can be used as a diagnostic tool in burn sepsis.

Meta-analysis by cabral[14] in 2016 shows PCT having a better ability to discriminate non septic patients from septic patients. [13, 4] Previous studies performed on role of PCT in sepsis suggest a cut off value ranging from 0.5ng/ml to 3.0ng/ml .The cut off value in our study (2.1ng/ml) falls in the feasible range with the previous studies[4,13,15] . We did not observe any correlation between PCT concentrations at the time of admission and TBSA as per conclusion by Von Heimberg et al [16]. We observed significant increase in PCT in septic patients compared to their preseptic levels .The median PCT concentrations were 2.45 ng/ml in septic patients at the time of admission and 8.50ng/ml during the septic episode.

PCT concentrations are also reported to be influenced by the organism responsible for causing bacterimia[17]. Appropriate antibiotic therapy is reported to cause rapid decline in PCT levels [18].In our study we estimated the response in two patients who survived after sepsis after the up gradation of antibiotics. Due to the high cost of the test, it is difficult to perform PCT estimation on daily or biweekly basis .Hence the time of PCT estimation was also decided after going through the literature before the start of study. Sepsis is unlikely in 20-30% TBSA involvement, so we considered the patient population with more than and equal to 30% TBSA burn. The Limitation of the study is the cost of PCT and its role in diagnosing the sepsis only.

Conclusion:

Early diagnosis and initiation of treatment for sepsis remains a crucial aspect of burn care .PCT is a reliable and quick diagnostic biomarker in burn sepsis. Hence it is the need of the hour that it should be added as an adjunct biomarker to the already followed ABA guidelines 2007 for diagnosis of burn sepsis.

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Table 1: The Median and the distribution of procalcitonin in sepsis and non sepsis group

	Median	N	SD
Group A (Sepsis)	8.50	28	20.86
Group B (No sepsis)	1.85	24	19.19
Total	4.20	52	20.42

Table 2: The Performance of Procalcitonin in sepsis

Characteristics	Values
Cut off value (ng/ml)	2.1
Sensitivity (%)	89.29
Specificity (%)	58.33
PPV (%)	71.43
NPV (%)	82.35
AUC	0.78
95% CI	
Lower	0.645
Upper	0.914
Positive likelihood ratio	2.14
negative likelihood ratio	0.18

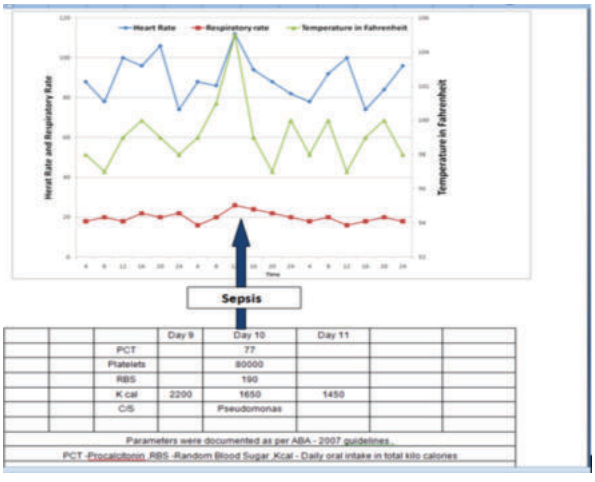

Figure 1: Sample case {Arrow indicate sepsis episode and respective procalcitonin level)

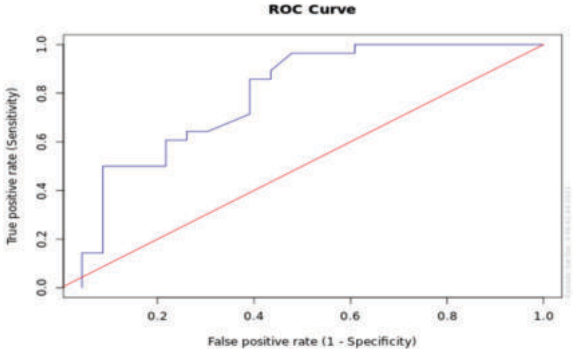

Figure 2: The diagnostic performance of procalcitonin in sepsis as being assessed by Receiver operating characteristic curve (ROC) curve

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