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VALUE OF PROCALCITONIN AS A PROGNOSTIC BIOMARKER OF SEPSIS IN BURN INJURED PATIENTS OF A TERTIARY HEALTHCARE CENTRE (OSMANIA GENERAL HOSPITAL)

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ABSTRACT

Introduction: The leading cause of mortality in burn injured patients is sepsis, accounting to 34.4% of deaths according to a recent study [(1)]. The loss of cutaneous barrier allows microbes to easily enter the body and cause skin and blood borne infection [(2)]. Some studies have reported that Procalcitonin is a useful marker for sepsis in severe burn injury [(16,17)]. Therefore, this study is an to attempt to assess the clinical significance of procalcitonin in burn patients as an early indicator of sepsis. **Aim:** To study the value of Procalcitonin levels as a prognostic biomarker for sepsis in thermal burn injured patients.

Material And Methods:

Type Of Study: Observational study

Study Duration: 2 months

Study Design: Cross-sectional study.

A total of 25 subjects of burns were included in this study. Burn injured patients with burn size 20- 50% TBSA and age 18-50 years old, admitted in Plastic Surgery in-patient department were included in this study. The study was conducted in a Government tertiary care hospital, Hyderabad. Blood samples were obtained from each patient for measurement of serum procalcitonin(PCT)) after 48 hours (day 3) after the burn injury and at 120 hours (day 5). **Results:** With increasing TBS burn involvement there is gradual increase in ProCalcitonin levels which was found to be significant on Day 3 and Day 5 with p value of 0.048 and 0.005 on Day 5 respectively by ANOVA test. **Conclusion:** Procalcitonin can be used as a reliable and predictive biomarker for the early diagnosis of sepsis in burn injured patients.

KEYWORDS

burns, infection, sepsis, blood culture, Procalcitonin, antibiotics.

INTRODUCTION:

The leading cause of mortality in burn injured patients is sepsis, accounting to 34.4% of deaths according to a recent study [1]. The loss of cutaneous barrier allows microbes to easily enter the body and cause skin and blood borne infection [2]. The simultaneous massive release of inflammatory mediators in burn patients often masks the signs of sepsis which can otherwise be recognized easily.[3]

Therefore, in burns patients, the chance of developing sepsis is high and the possibility of diagnosing it accurately and at the right time is difficult. The purpose of this study is to identify a biomarker that can predict sepsis accurately in burns patients better than the available clinical/laboratory methods in use currently.

Blood culture for micro-organisms is the present gold standard for diagnosis of sepsis. This test takes up to 72 hours and may be unreliable due to prior administration of antibiotics and many factors such as contamination [4].This delay in diagnosis can result in delay in treatment and result in rapid progression to circulatory collapse, multiple organ dysfunction syndrome (MODS) and finally death.[5]

Use of antibiotics in burns patients who do not have sepsis but one suspected to have first evidence of infection was practiced previously as a preventive measure. This indiscriminate use has lead to the development of antibiotic resistance and formation of superbugs, making even highest antibiotics ineffective.

The importance of finding a balance between too early treatment and delayed diagnosis cannot be emphasized. Inflammatory biomarkers are proteins produced in the body in the response to infection. CRP is one such biomarker which is commonly used to detect sepsis ;but it can also be raised in many other conditions like trauma, tissue necrosis etc.; burn injury itself without sepsis can lead to raised CRP levels, making it a very nonspecific marker and thus limiting its use.[6,7,8]

Procalcitonin (PCT) ,116-amino acid prohormone of calcitonin, secreted by thyroid -C cells, has recently been identified as one of the earliest possible markers of the sepsis in burn injured patients. In healthy individuals, PCT level is barely detected in blood [<0.01 ng/ml]. Many other cell types (liver, kidney, adipocytes) secrete PCT during septic episodes and it is massively released into the blood stream at concentrations that reach 1000 times its normal values.[9]

Increased PCT is noticeable 2-4 h after sepsis onset and peaks at 24-48 h. PCT levels decrease by 50% every 25-30 h (half-life) when the infectious process is controlled. Peak levels correlate with the severity

of infection, with higher levels observed in patients with septic shock and sepsis [10,11] PCT level can also be helpful in determining the appropriate duration of antibiotic therapy. [12,13,14,15]

Therefore, some studies have reported that Procalcitonin is a useful marker for sepsis in severe burn injury [16,17]. However, this has been debated by others. [18,19,20,21] This scenario complicates the diagnostic use of procalcitonin levels in burn patients.

Therefore, this study is an to attempt to assess the clinical significance of procalcitonin in burn patients as an early indicator of sepsis.

REVIEW OF LITERATURE-

- Many studies have been done to assess the value of Procalcitonin level during sepsis episode. A few of the relevant studies are cited below.
- Mokline A et al.[17] conducted a prospective study with age range of 20-54yrs and divided the patients into 2 groups -septic and non-septic according to ABA sepsis guidelines and observed that PCT levels(cut off >0.69 ng/ml) were higher in patients with sepsis. On day 5 postburn, peak PCT levels were significantly higher in septic patients.PCT had a sensitivity of 89% and specificity of 85%.They found that among sepsis patients there was a prominent increase of the PCT level when gram negative organisms were isolated in blood culture compared to gram positive.PCT has a potential of affecting diagnosis and prognosis of sepsis in burned patients favourably and also helps in monitoring the response to antimicrobial therapy.
- Kumar HR et al.[22] conducted a prospective study in 33 patients with an age range of 17- 59yrs over a period of 9 months and according to ABA guidelines ,patients were divided into septic and non-septic.The study showed that PCT had high sensitivity(94.7%) and specificity(85.7%) to diagnose sepsis in burns and has a potential to bridge the existing gap between clinical signs and confirmatory culture report.
- Kundes MF et al.[23] did a retrospective study with TBSA range 1-49%. They found that PCT levels > 0.5ng/dl had 100% sensitivity and 83% specificity for predicting septiceamia.
- Luis Cabral et al.[24] study showed that PCT kinetics may aid in the differential diagnosis between true sepsis and the normal inflammatory response to burn trauma in the first 5 days after burn injury. They diagnosed sepsis according to ABA guidelines and PCT was evaluated during first five days after burn injury and during the five days after the surgery. Statistically significant difference was found between the group of patients who developed at least one episode of sepsis during initial 5 days of postburn and those who did not develop sepsis. The PCT values > 1.00ng/ml clearly associated with septic processes.
- A study done by Barathi et al.[6] concluded that PCT is a highly efficient laboratory parameter involving a simple and rapid bedside test for diagnosis and prognosis of severe infectious complications after burn. They found PCT had 100% sensitivity and 89.33% specificity.
- Rui-Xin Wu 1 et al.[25] study included 24 burn patients and it showed that PCT can be helpful in determining the septic shock and blood stream infection in burn patients but CRP levels, platelet count and WBC were of little diagnostic value. Patients with bacteremia had significantly elevated PCT levels compared to patients without bacteremia.
- Cabral et al.[26] conducted a meta-analysis on PCT performance as a biomarker for sepsis. This meta-analysis showed PCT may be considered as a biomarker with a strong diagnostic ability to discriminate between the septic from the non-septic burn patients. Thus, this work encourages the determination of PCT levels in clinical practice for the management of these patients, in order to timely identify the susceptibility to sepsis and to initiate the antimicrobial therapy, improving the patients' outcomes.
- In contrary to all these studies, there are some studies which has shown the negative implications on PCT level compared to other markers. Like the study done L.Bargues et al[18], they concluded that PCT does not offer a significant advantage for diagnosis of sepsis in burns, compared with the other biological markers like CRP, WBC. In their study CRP has more sensitivity and specificity in diagnosing sepsis in burns.

AIMS AND OBJECTIVES-

AIM: To study the value of Procalcitonin levels as a prognostic biomarker for sepsis in thermal burn injured patients.

OBJECTIVES:

- To measure the value of serum procalcitonin (PCT) in thermal burn injured patients as an early indicator of sepsis.
- To correlate blood culture with PCT in the same patients.

MATERIAL AND METHODS:

Type Of Study: Observational study

Study Design: Cross-sectional study.

Study Site: Department of Plastic & Reconstructive Surgery, Osmania medical college/Osmania general hospital, Hyderabad, Telangana, India (Government tertiary care hospital)

Study Duration: 2 months

Study Population: Thermal Burn injured patients admitted in Government tertiary healthcare Centre, who fit into the inclusion criteria.

Sample Size: All the burn injured patients who fulfilled the inclusion criteria, admitted to Government tertiary care hospital during the study period of 2 months were included in this study. At the point of study, 25 patients from Plastic surgery department who satisfy the criteria for study were taken as sample size.

Selection Criteria-

Inclusion Criteria:

- Patients with thermal burn area 20-50% total body surface area (TBSA)
- Patients aged 18-50 years old.
- Patients who have given written consent.

Exclusion Criteria:

- Patients with comorbid illnesses like diabetis mellitus, coronary artery disease and collagen vascular diseases.
- Patients with immunocompromised condition.
- Patients with electrical and chemical burns.
- Patients with infections prior to the burn injury.
- Patients with thermal burn area <20%TBSA.

INSTRUMENTS:

- Data Collection Sheet.
- Vacutainers for collection of blood samples.
- Brain Heart Infusion broth bottle for collection of blood for blood culture.
- Automated analyser -SEIMENS Advia Centaur immunoassay system.
- Serum Procalcitonin CLIA(Chemiluminescence immunoassay) kit.

MATERIALS AND METHODS

A total of 25 subjects of burns were included in this study. Ethical clearance was obtained from institutional ethics committee. Informed consent was taken from all patients after explaining to them the purpose of the study in their native language. Burn injured patients with burn size 20- 50% TBSA and age 18-50 years old, admitted in Plastic Surgery in-patient department were included in this study. The study was conducted in a Government tertiary care hospital, Hyderabad.

Blood samples were obtained from each patient for measurement of serum procalcitonin(PCT)) after 48 hours (day 3) after the burn injury and at 120 hours (day 5). Routine investigations like platelet count, blood glucose level were done in the clinical Biochemistry laboratory and the data was obtained from case sheets.

Every day for initial five days, all patients were examined for the signs of sepsis. Sepsis was defined according to the American Burn Association Criteria for the presence of infection:[27]

PARAMETERS	IN ADULTS
Temperature	>39°C or <36.5°C
Progressive tachycardia	>110 beats per minute(bpm)
Progressive tachypnea	>25 bpm(not ventilated) or >12 L/min(ventilated)
Thrombocytopenia (applicable only 3 days after initial resuscitation)	<100,000/uL

Hyperglycemia(without preexisting diabetis mellitus)	>200 mg/dl(without treatment) or insulin resistance: >7 IU/hour IV insulin
Inability to continue enteral feedings 24 h	Abdominal distention, Enteral feeding intolerance (residual two times feeding rate), Uncontrollable diarrhea
Presence of infection clinically or microbiologically documented.	

Meeting more than 3 of these criteria should "trigger" concern for infection. All the parameters necessary to diagnose burns sepsis according to American Burn Association (ABA) consensus were documented in a Data Collection Sheet from the data obtained from case sheets. This is the reference standard of this study.

Blood samples were sent to Microbiology laboratory for culture on Day 5 from patients with clinical symptoms of infection. For blood culture, 5-7ml of blood is dispersed into 25ml Brain heart infusion broth bottle and sent to Microbiology laboratory. It is then incubated in bacteriological incubator at 37^0C for 7 days. With due help from Microbiologist, subcultures were done onto Blood agar or MacConkey agar and incubated overnight in bacteriological incubator at 37^0C.Any growth on media was identified by Gram's stain and standard biochemical identification tests.

Procalcitonin Estimation-

Serum procalcitonin(PCT) estimation was done in clinical Biochemistry department laboratory.2-3 ml of blood was collected in a vacutainer from patient and the blood was allowed to clot before centrifugation. Then it is centrifuged at 2000-3000 rpm for 5 min to separate serum. With due support from the Biochemist, PCT was then estimated using serum procalcitonin CLIA kit (SIEMENS) which contains 1 Ready pack with primary reagent pack containing ADVIA Centaur BRAHMNS PCT Lite reagent and solid phase, Ancillary reagent pack and calibarators. Advia Centuar BRAHMNS PCT quality control was used along with the test as internal quality control.

The results were obtained within 20 min of the test. Test result was read using ID marked magnetic base racks with centrifuge tubes in Seimens Advia Centaur immunoassay system.

STORAGE-

1.If the serum sample was not assayed same day, then serum aliquots were stored at -20^0C. 2.PCT CLIA kit and reagents were stored at 2-8^0C.

Data Collection And Analysis:

Data collection was done after obtaining the clearance from the Institutional Ethical committee. Data was compiled in Microsoft excel and analysed using Epi -info 7.2 software. P value was considered as significant at a value of less than 0.05 at 95% confidence interval. Anova test and Student's unpaired t-test were used in this study for analysis**.**

OBSERVATION AND RESULTS-

A total of 25 thermal burn injured patients(n=25) were included in this study with a mean age of 35.2yrs**.** (Age range18-50yr). Among them 15 were males and 10 were females with 20-50% TBSA of burns. The mean percentage of TBSA of burn was 33.56% .

Total of 50 samples for procalcitonin estimation were analysed from 25 patients (on Day 3 and Day 5 from each patient).

The cut off value of PCT was taken as 0.5ng/ml. The mean value of PCT in sepsis and non-sepsis was 3.67±4.21 vs 0.21±0.29 respectively with a significant P value of 0.00759 on Day 3 and was 16.7±20.13 vs 0.409±0.18 respectively with a significant P value of 0.00733 on Day 5. (Student's unpaired t-test for evaluation).

According to American Burn Association criteria 15 out of 25 were grouped as sepsis. Among these patients, 11 patients had elevated PCT levels.The blood culture was positive in 4 of 15 sepsis patients. The organisms isolated were Klebsiella in 2,Psedomonas in 1, Enterobacteriace in 1.

Table 1:Age Distribution Among The Study Group-

Age range of 18-50yrs was taken and mean age was 35.2 yrs.44% of patients were in the age group 40-50yrs.

AGE	n=25	PERCENTAGE
18-28yrs	9	36%
29-39yrs	5	20%
40-50yrs	11	44%

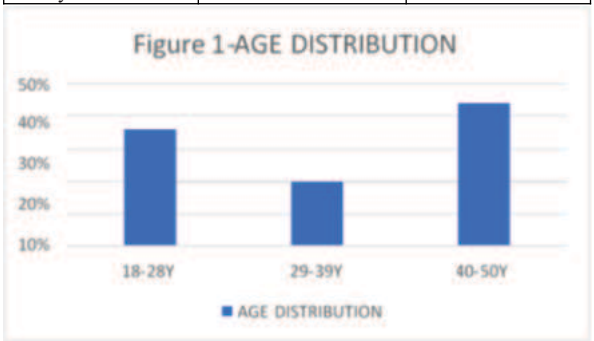

Table 2: Distribution Of Sex-

Among total of 25 cases, 60% were males and 40% were females.

	PATIENTS	PERCENTAGE
MALE	15	60%
FEMALE	10	40%
TOTAL	25	100%

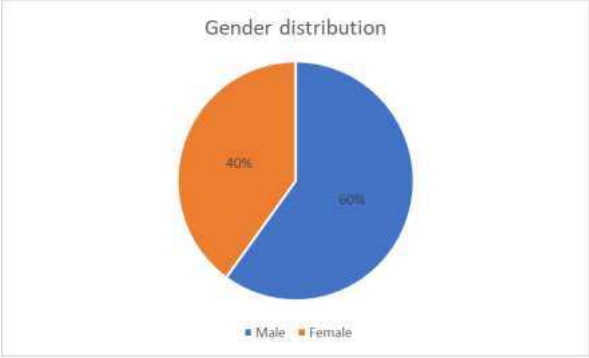

Figure 2-Pie Diagram Representing Gender Distribution.

Table 3: Percentage Of Burns-

44% of patients had burns from 20-30% Total body surface area.
24% had burns from 30-40%TBSA and 32% had burns from 40-50%TBSA.

TBSA	n=25	PERCENTAGE
20-30%	11	44%
30-40%	6	24%
40-50%	8	32%

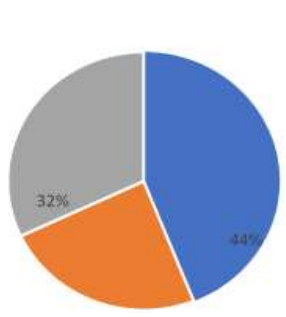

Figure 3- Pie Diagram Representing Percentage Of Burns-

Table 4: Development Of Sepsis In Study Population-

Among 25 patients,15 patients fulfilled the American Burn Association Criteria for sepsis.

	n=25	PERCENTAGE
WITH SEPSIS	15	60%
WITHOUT SEPSIS	10	40%

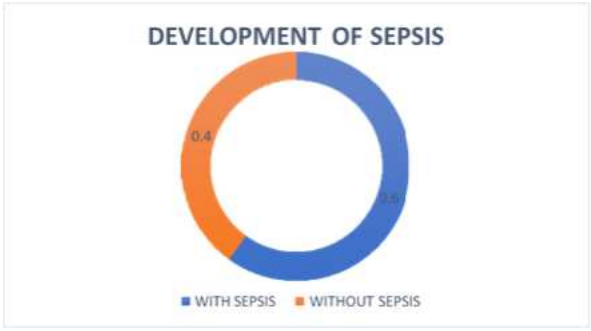

Figure 4- Development Of Sepsis In Study Population-

Table 5: Procalcitonin And Sepsis-
Among 15 pateints with sepsis ,PCT (>0.5ng/ml)was elevated in 11 patients.

	WITH SEPSIS	WITHOUT SEPSIS
PCT POSITIVE (>0.5ng/ml)	11	2
PCT NEGATIVE (<0.5ng/ml)	4	8

Table 6: Diagnostic Performnace Of PCT For Sepsis-
PCT showed a high sensitivity of 73.3% in the diagnosis of sepsis.

VARIABLES	SEPSIS
SENSITIVITY (%)	73.3%
SPECIFICITY (%)	66.6%
POSITIVE PREDICTIVE VALUE (%)	84.6%
NEGATIVE PREDICTIVE VALUE(%)	80%

Table 7: Blood Culture Isolates-
Blood culture was sent from 15 patients with clinical symptoms of infection. Among 15 patients,4 had positive blood culture and all gram negative organisms were isolated. Elevated PCT levels were observed in blood culture positive patients on DAY 5.

BLOOD CULTURE ISOLATES	NUMBER
Klebsiella species	2
Pseudomonas species	1
Enterobacteriaceae	1
TOTAL	4

Table 8: Total Number Of Positive Pct And Blood Culture-

Total patients (n)	SEPSIS PATIENTS	PCT Positivity>0.5ng/ml	Blood Culture Positivity
25	15	11	4

Table 9: Correlating Mean Pct Values With TBSA Of Burns
There was a correlation between the percentage of burns and mean PCT values with higher values noted on Day 5.40-50% of TBSA of burns had a mean PCT value of 3.99 on Day 3 and 24.8 on Day 5.

TBSA(%) Of Burns	Procalcitonin mean values DAY 3	Procalcitonin mean values DAY 5
20-30%	0.33	0.41
30-40%	3.68	8.56
40-50%	3.99	24.8

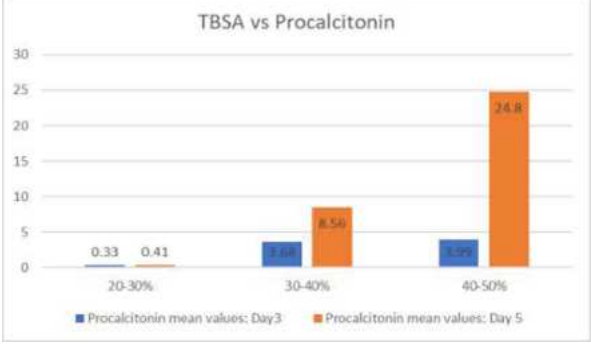

Figure 5- Bar Diagram Representing Correlation Between Mean PCT Values And TBSA Of Burns

With increasing TBS burn involvement there is gradual increase in PCT levels which was found to be significant on Day 3 and Day 5 with p value of 0.048 and 0.005 on Day 5 respectively by ANOVA test.

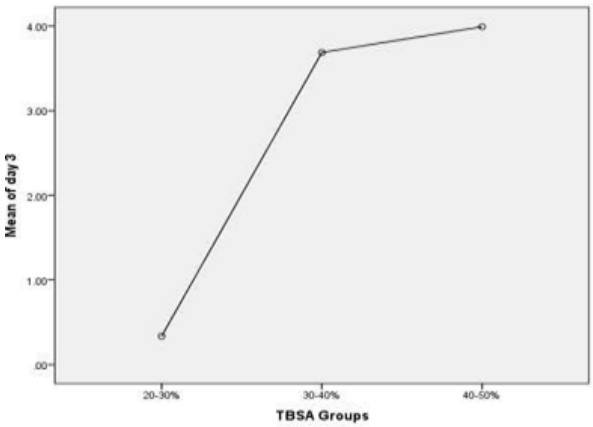

Figure 6- Graph 1- Correlation of Mean PCT values with TBSA of burns on Day 3

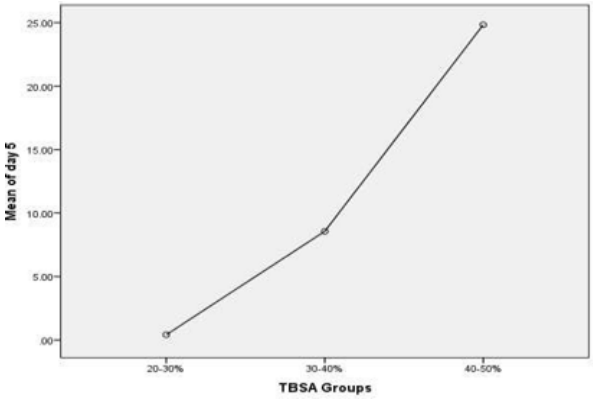

Figure 7- Graph 2-Correlation of Mean PCT values with TBSA of burnss on Day 5

DISCUSSION:
Sepsis is the leading cause of mortality in thermal burn injured patients[1]. Sepsis is defined as systemic inflammatory syndrome (SIRS) commonly induced by bacterial infection. Delay in diagnosis can result in delay in treatment and result in rapid progression to circulatory collapse, multiple organ dysfunction syndrome (MODS) and finally death[5]. However, the possibility of diagnosing it accurately and at the right time is difficult as there is a simultaneous massive release of inflammatory mediators in burn patients which often masks the signs of sepsis[3]. Henceforth, in the present study, a biomarker procalcitonin was estimated in thermal burn injured patients as an early indicator of sepsis.

AGE:
In this study, mean age of 32.5yrs (age range 18-50 years) was considered which was similar to the study conducted by Mokline A et al.[17] with age range of 20-54 years and by Kumar HR et al.[22] with age range of 17-59yrs. It was noted that thermal burn injury was significantly higher in productive age group.

TBSA:
In this study, 20-50% TBSA of burns was considered with mean TBSA of 35% whereas in a study conducted by Kumar HR et al.[22] mean TBSA was 48% and by Von Heimburg D et al.[27] mean TBSA was 51% (20-91%).

In the current study, episode of sepsis was found markedly in patients with TBSA 30-50%.

High TBSA of burns correlated with peak mean PCT levels. Similar results were found in a study conducted by Von Heimburg D et al.[27]. Significantly higher PCT levels (mean 24.8) were observed on postburn Day 5 with TBSA 40-50%.

PCT:

In this study, PCT cut off value of 0.5ng/ml was taken into consideration.PCT levels among patients in sepsis showed sensitivity of 73.3% and specificity of 66.6%.

Where as in Mokline A et al.[17]study they found PCT value greater than 0.69ng/ml was significant as a marker of sepsis and their study showed sensitivity of 89% and specificity 85%. Kundes MF et al.[23]considered that a PCT value >0.5ng/ml which is similar to this study had 100% sensitivity and 83% specificity in predicting septicaemia.

	SENSITIVITY	SPECIFICITY
Mokline A et al study	89%	85%
Kumar HR et al study	94.7%	85.7%
Kundes MF et al study	100%	83%
Present study	73.3%	66.6%

PCT levels elevated significantly in sepsis patients than in non-sepsis patients. On day 5 postburn, strong significant difference is seen between septic and non-septic patients. Peak PCT levels were higher in septic patients at day 5(day of diagnosis sepsis). Similar results are found in a study conducted by Mokline A et al.[17].

Blood Culture:

Blood culture was 26.6% positive. This shows that sensitivity is low for blood culture, though it was considered a gold standard. It might be due to prior administration of antibiotics.

High PCT levels were observed in patients with positive blood culture. All gram negative organisms were isolated in blood culture.Wu RX et al.[25]study reported that the PCT levels significantly increased in burn patients with blood stream infection than in burn patients without these conditions.

Mokline A et al.[17] study reported that in septic patients there was a prominent increase of the PCT level when gram negative organisms were identified as opposed to gram positive.

Limitations Of The Study:

1) The sample size is small to correlate to regional and national level trends.
2) Cost-effective analysis of various diagnostic and treatment modalities was not conducted.
3) Long term follow up and course of patient was not discussed.

CONCLUSION:

As observed from the study, following points can be concluded-
1) Procalcitonin is significantly elevated in burn patients developing sepsis when evaluated at Day 3 and Day 5 of hospitalization.
2) Estimation of procalcitonin as a marker of sepsis in burn patients carries a high sensitivity at 73.3%.
3) Procalcitonin can be used as a reliable and predictive biomarker for the early diagnosis of sepsis in burn injured patients. The approach can help in identifying such patients and starting early antibiotic therapy thereby leading to better patient outcomes and thus reducing morbidity and mortality. This can be really helpful in patients with negative blood cultures.

However, more comprehensive and prospective studies may be required to validate this finding.

SUMMARY-

In burns patients, early diagnosis of sepsis accurately and at the right time is difficult. Hence to assess the value of procalcitonin as an early indicator of sepsis, a cross sectional analytical study was done in thermal burn injured patients. 25 patients were examined for initial 5 days of post burn injury. Meeting more than 3 of the American Burn Association criteria,15 patients were grouped into sepsis. Procalcitonin was evaluated on Day 3 and Day 5. Significantly higher PCT levels(mean PCT - 24.8 ng/ml) were noted on post burn Day 5 in sepsis patientswith TBSA 40-50%. The sensitivity and specificity of PCT was 73.3% and 66.6% respectively. Though blood culture is the present gold standard for diagnosis of sepsis, it had low sensitivity in this study. Higher PCT levels were observed in blood culture positive patients. Thus PCT can be used as a prognostic biomarker of sepsis in thermal burn injured patients.

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